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Surgical Treatment of Mitral Stenosis and Aortic Stenosis

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MITRAL STENOSIS

MITRAL VALVOTOMY, or mitral commissurotomy, has over the last 10 years proved to be one of the most valuable operations of modern surgery. Even if it does not cure, and although many patients are still left with other effects of rheumatic heart disease and past effects of a stenosed mitral valve, after a successful operation the clock is put back to the time before severe incapacity developed and an enjoyable and productive life is once more possible. Surgical treatment has now been established long enough to give some indication of its efficacy both in degree and in time.

The stenosed mitral valve is an obstruction to the circulation which increases the work of the heart, like obstruction in other organs of the body which can only be dealt with surgically. This logical treatment was first attempted in the 1920s, but the pioneer surgeons—Cutler and associates (30, 31), Allen and Graham (1), Pribram (65), and Souttar (69)—were all forced to abandon operative treatment because of a lack of early success in a climate of medical scepticism; the time was not yet ripe. After the Second World War, advances in thoracic surgery, in postoperative care, anesthesia, and blood transfusion, and the advent of antibiotics and an awakened interest in the hemodynamics of the heart resulting from the development of cardiac catheterization led to success on both sides of the Atlantic. Bailey and associates (3, 5) in Philadelphia, Harken and co-workers (42) in Boston, and Brock and associates (12) in London, reintroduced surgical treatment of mitral stenosis. The technic adopted by Bailey and by Brock which estab-

lished the present-day operation was essentially the same as that used by Souttar in 1925.

The early results were impressive and the operative mortality was not prohibitive—not always the case in pioneer cardiac surgery—so that in a few years the operation rapidly became widely established, and the demands of patients overcame the hesitancy of the most conservative and sceptical. Surgical treatment emphasized the many gaps in the knowledge of this common disease and stimulated clinical, hemodynamic, and pathologic research which has increased cardiologic knowledge generally. Furthermore, the success of mitral valvotomy paved the way for advance in the surgical treatment of other intracardiac lesions, both congenital and acquired, so that within 10 years most have come to be considered curable or remediable either now or in the not so distant future.

The operative mortality in the earliest reported series was between 10 and 15 per cent, which is very high by modern standards. Operative mortality was naturally higher before the surgical technic was perfected, partly because the proportion of severe cases was higher before surgical treatment had become routine. Even in those early days, the mortality for an emergency operation in a crippling and killing disease compared favorably with other established operations. Today, the operative mortality should not exceed 5 per cent, even when the most severe cases are accepted, and in our own experience over the last few years is under 2 per cent. There is probably more danger that the diminished surgical risk may encourage unnecessary operations on patients with rheumatic heart disease but without tight mitral stenosis, or on patients with signs of mitral stenosis but no true disability, than that the patient who really needs mitral valvotomy, however advanced his disease, will succumb from operation.

IMMEDIATE RESULTS OF OPERATION.—Many patients are conscious of improvement immediately after operation, despite the attendant discomforts of a thoracotomy; they are aware of an increased warmth of the extremities—"an improved circulation"—and particularly of a lessening of tension in the lungs which corresponds to the lowered pressure in the left atrium observed at operation after successful valvotomy. Those with marked pulmonary hypertension may not experience maximum benefit until some months after operation, and it has been shown that the pulmonary pressure may take this time to drop to its lowest level. These patients, and those with associated organic tricuspid disease, may show transient congestive failure in the postoperative period. The only postoperative complication that needs mentioning is the so-called postcommissurotomy or postvalvotomy syn-

drome. The features of the syndrome are fever, chest pain, pericardial effusion which may cause marked increase in the size of the heart (as shown by radiography) and increased venous pressure, pleural effusion particularly on the left side, electrocardiographic changes, and anemia not explained by blood loss at operation; about half of the patients experience it in minor or major degree. It may happen immediately after operation, may be delayed several weeks or months, and may recur during the first year. Its recognition is important because patients may then be warned that the good of the operation has not been undone, as they are naturally apt to think, and that it is consistent with an excellent result. The term "postcommissurotomy (or postvalvotomy) syndrome" is bad, as the syndrome is not confined to this operation, nor is it associated with an exacerbation of rheumatic activity, as was first thought. It occurs after other operations in which the pericardium is opened, as in congenital heart disease, and the same reaction was noted by Wood (71) during the Second World War, associated with foreign bodies in the pericardium. It is a nonspecific inflammatory reaction, and "postpericardectomy syndrome" is the best term to describe it. It is usually self-limited, lasting less than a week, but occasionally may prolong the postoperative period for several weeks. The pain and fever are relieved by aspirin, though in severe or prolonged bouts cortisone may be indicated.

LATE RESULTS OF OPERATION.—There is general agreement among the reported series, recently reviewed by Baden (2), that between 70 and 80 per cent have good or excellent results after valvotomy, though the criteria for this assessment are not always clear. Even when improvement is less than this, due either to inadequate relief of stenosis or to the presence of regurgitation, most patients are grateful for relief of symptoms. The psychologic effect of successfully weathering a major operation and the increased rest of the convalescent period may delude the uncritical physician into thinking that a good result has been obtained when little has been achieved surgically. Although a reasonable functional result may be achieved without marked alteration in physical signs, in those with excellent results there is a striking change. The diastolic murmur may be heard only with difficulty or not at all, though the opening snap rarely disappears. There is a diminution or disappearance of right ventricular hypertrophy and of the "mitral" P wave, if these were present before operation. Radiographic signs of pulmonary hypertension and pulmonary venous congestion diminish, though marked decrease of heart size is uncommon. Improved nutrition is obvious, and marked gain in weight is common. The liability to "chestiness" in cold and wet weather is lessened.

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For a proper appraisal of the result of mitral valvotomy, a careful follow-up is essential to observe how long improvement is maintained and to what degree the natural history of the disease is changed. Of paramount interest is restenosis of the valve. As it may take many years for the stenosis to develop to the critical level which produces disability, the period of follow-up is still too short to decide the incidence of restenosis in those whose valves were fully opened at operation. The medical literature is not rich in detailed studies on the long-term effect of mitral valvotomy, so that I prefer to discuss a personal series from Guy's Hospital. It has the advantage of an early start, includes a high proportion of severe cases, and is limited to the first 200 patients, which enabled one physician to know the patients individually and observe them carefully.

Follow-Up of Patients after Mitral Valvotomy

Nature of follow-up.—Of 239 consecutive patients who underwent operation, 7 were operated on for mitral regurgitation, 27 (11.7 per cent) died as a result of operation, and 5 could not be followed. The remaining 200 patients, in November, 1958, had been followed for:

Number of Patients	*Years after Operation*
1	10
2	9
5	8
28	7
62	6
102	5

Most of the 27 operative deaths occurred early in the series, giving a high mortality rate compared with present figures. Functional change assessed by symptoms—and this is very individual and varies with the patient's environment and temperament—was correlated with signs, including repeated radiographic and electrocardiographic evidence. Catheterization was performed preoperatively in 96 patients, postoperatively in 44, and repeated more than once in 13. Disability was assessed before and after operation and during the follow-up period, using the same grading system. Before operation, the 200 patients were assessed as follows:

Grade	*Number of Patients*
0: No disability	None
1: Symptoms only on marked exertion	None
2: Symptoms on mild exertion; able to carry on normal activity with difficulty	28
3: Incapacitated enough to interfere with work and liable to episodes necessitating bed rest or hospitalization	128
4: Totally incapacitated	44

Patients were first assessed 1 year after operation to ensure that they had passed through a winter, the testing season for mitral subjects. Improvement by 3 or more grades was considered an excellent result, by 2 grades a good result, by 1 grade a fair result, and no improvement a poor result. Patients were assessed each year of the follow-up, but many, particularly those with unsatisfactory results or whose state was deteriorating, were seen at more frequent intervals.

FOLLOW-UP RESULTS.—At the end of 1 year, results were considered excellent in 66, good in 104, fair in 20, and poor in 10. The excellent and good results, grouped together as "good results," comprised 85 per cent of the series. It is not surprising that of the 30 patients with poor results (20 fair, 10 poor), only 5 did not deteriorate further and 16

TABLE 1.—RESULTS IN TOTAL FOLLOW-UP PERIOD

CLINICAL ASSESSMENT AT END OF ONE YEAR		SUBSEQUENT FOLLOW-UP Deteriorate (Die)	Remain the Same
Poor and fair results	30	25 (16)	5
Good and excellent results	170	51 (12)	119
Totals	200	76 (28)	124

died, since the operative result was poor in more than half of them (Table 1). But it is surprising that during the years of follow-up 51 (30 per cent) of the 170 patients considered as good and excellent clinical results at the end of the first postoperative year should have deteriorated and 12 died. This group of patients is of particular interest in comparison with those who maintained their improvement. Factors which might be cited to explain the deterioration are: *(1)* the operative result might have been incorrectly assessed; *(2)* restenosis of the valve; and *(3)* causes other than mitral stenosis.

There was a steady proportion of deteriorating patients (5 per cent) in each of the first 5 years, and a higher proportion in the 2 subsequent years (Fig. 1). The latter is probably due to the larger number of incomplete valvotomies and the extreme disability in the early cases. This assumption is supported by a further year of follow-up (to November, 1959), which shows 63 per cent of good results 6 years after operation, a fall of only 3 per cent from the fifth year. The patients who deteriorated were the ones with some degree of disability after operation, while the proportion of those with excellent results (no disability) remained constant (Fig. 2). Although the number of deaths increased with each year, there were never more than 2 per cent of patients with total incapacity (grade 4) in the follow-up period, whereas before operation 22 per cent were in this category. This means

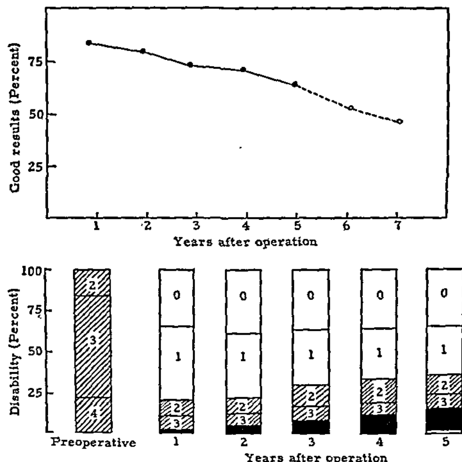


FIG. 1 (above).—Percentage of good results (improvement by 2, 3, or more grades) in 200 patients, 110 of whom have been followed for 5 years, 62 for 6 years, and 28 for 7 years.

FIG. 2 (below).—Disability preoperatively and for 5 years of follow-up after operation. The percentage of patients with grade 4 disability in the follow-up period was too small to show graphically. Black area, death in the follow-up period. The lowest white area in column 5 indicates re-operations.

that those patients who deteriorated after operation maintained some activity until their final illness and did not revert to a chronic state of total incapacity which was common before mitral valvotomy. Undoubtedly they had the advantage of improved medical treatment, but a correct interpretation, I think, is that the operation gave them a new lease of life and they were determined to use it to the full, even if it was limited.

Degree of Valvotomy Related to Results

Not only the immediate result but the maintenance of improvement is determined by the degree of success achieved by the surgeon. The surgeon's impression of the anatomic results of the operation have been graded for comparison with the grades of clinical improvement (see Table 2). The 4 grades of operative results are:

1, poor: At most, a widening of the stenosed valve, but not beyond the area of critical tendon insertion (18).

2, fair: A widening of the mitral orifice without full opening of either commissure.

3, good: Full opening of one commissure.

4, excellent: Division of both commissures, leaving a full opening and a reasonably mobile valve.

TABLE 2.—Clinical Results of Mitral Valvotomy Related to Anatomic Results of Operation

Clinical Results	Operative Results, Grade 4	3	2	1
Improvement by 2 or more grades (excellent or good, 119 patients)	72	40	6	1
Deterioration (51 patients)	9	15	21	6
Improvement by 1 grade or no improvement (fair and poor, 30 patients)	0	3	11	16
Totals	81	58	38	23

The assessment was made from the surgeon's full report, dictated immediately after operation, which was always available. Its importance cannot be overstressed, since without it no prognosis after operation can be attempted and, later, the assessment of restenosis or a decision to reoperate is difficult or impossible. The statement "a successful operation was achieved in all cases" which may be found in the literature is meaningless and negates any conclusions, even when these are supported by careful hemodynamic measurements.

The clear correlation between the anatomic success of the operation and the permanence of the clinical results in our series of cases is shown in Table 2. Only 7 patients out of the 119 who maintained their excellent or good clinical results had had inadequate operative results (grades 1 and 2). Of the 51 who deteriorated after an initially good clinical result, 21 had had grade 1 or 2 operative results. In the 30 patients with poor clinical results, the operative results were poor or fair in 27. There was a higher proportion of inadequate operations in

the early part of the series, and the proportion of later deteriorations is also higher (see Fig. 1).

RESTENOSIS.—Of the 30 patients assessed as having fair or poor results 1 year after valvotomy, 25 deteriorated subsequently and 16 of them died. In all but 2 of the 30 patients, clinical results were unsatisfactory because gross distortion of the valve mechanism, with calcification in 14, made successful valvotomy impossible, and they were left with a combination of stenosis and regurgitation or with severe regurgitation. The effects of cerebral embolism in the 2 patients with good cardiac function after operation placed them in this group. Some slight increase of stenosis may have occurred in 3 patients, but restenosis was not considered to have occurred in the others. It was not found in 4 cases at autopsy or in 4 patients who underwent a second operation.

Restenosis is a more likely cause of the deterioration of the 51 patients who originally had good or excellent results, but it was only established in 10 and considered a possibility in 5; there was no evidence of it in the other 36. In 8 cases, this could be assessed at autopsy; in 16, at reoperation; in 11, by cardiac catheterization; and in 16, by clinical evidence that the signs present before operation did not redevelop. In the 10 patients with established restenosis, the operation had at most comprised division of one commissure; since a completely opened, mobile valve was not achieved at operation, such a restenosis is only partial. Among the 119 patients who have maintained excellent or good results, a soft diastolic murmur has increased in some; this may indicate that restenosis is occurring, but in the only patient who has been recatheterized there was no evidence of stenosis and she showed the same excellent hemodynamic result as in the first postoperative catheterization.

Restenosis is an explanation often proffered when the result of mitral valvotomy is disappointing. Our figures of 10 established and 8 possible instances of restenosis, all partial, in 200 patients suggests that it is not common, or at least is a slow process. A poor result or early deterioration is usually due to an inadequate or unsuccessful valvotomy, and though the number of these diminishes with experience and improvements in surgical technics, a small proportion of failures must be accepted. Belcher (13), reporting on 12 reoperations from a series of 240 and reviewing the scanty literature concerning restenosis, makes the same distinction between deterioration after a good valvotomy which he calls true stenosis, though in only 1 patient of 4 with this diagnosis was the first operation "almost complete." The part played by inadequate valvotomy and restenosis in patients who deteriorate is

discussed fully, with hemodynamic data, by Baker and Hancock (10). There are, however, other reasons than restenosis why deterioration may occur after valvotomy, and these are apparent in our follow-up study.

Deterioration after Valvotomy in Presence of Complicating Disorders

Mitral regurgitation.—No patient with severe mitral regurgitation has been included in this series. Surgical treatment was attempted in 7 patients severely disabled with dominant regurgitation, but as no successes were achieved it was quickly abandoned. Ingenious maneuvers devised by surgeons to deal with this difficult problem have been reported, but their number and succession show that no solution has been found by "closed" operations. Dominant or pure regurgitation is associated with gross distortion of the valve and chordae tendinae, often with heavy calcification, and clearly needs "open" heart surgery; the future is therefore now brighter, though it will always be a more difficult surgical problem than the treatment of pure mitral stenosis.

TABLE 3.—Assessment of Mitral Regurgitation after Valvotomy

Clinical Results	Mitral Regurgitation		
	Significant	Mild	None
Excellent and good (119 patients)	12	28	79
Deterioration (51 patients)	15	6	30
Fair and poor (30 patients)	16	6	8
Totals	43	40	117

A mild degree of regurgitation is no contraindication to valvotomy, for a small regurgitant jet through a tightly stenosed orifice may be relieved by valvotomy if the valve is sufficiently mobile. Mild regurgitation was present in 15 patients, was relieved by operation in 4, and was only increased in 1. Significant regurgitation was found at operation in 14 patients, and in all the valve orifice was larger than in those with *pure stenosis; in no case was regurgitation abolished, and good results,* which have been maintained, were obtained only in 2 patients. Regurgitation after valvotomy was present in 83 patients, and was considered mild in 40 and significant in 43. This was often not apparent to the surgeon after valvotomy but was obvious later by auscultation, and by radiographic and electrocardiographic evidence in the more severe cases. Regurgitation both before and as a result of valvotomy is closely correlated with calcification of the valve.

The follow-up results in patients with and without regurgitation after valvotomy are shown in Table 3. Of those with significant regurgitation, less than a third have continued to show good results, compared with over two-thirds of those without regurgitation or with mild regurgitation. Regurgitation was thought to be a major factor in 16 of the 30 patients with poor results, and a factor in deterioration in 15 of the 51 patients who deteriorated after initially good results. In none of these was there any evidence of restenosis, as would be expected not only on account of the regurgitation but because of the wider orifice. On the other hand, in 3 patients with incomplete valvotomies a mild regurgitant murmur disappeared during the follow-up period and in all restenosis was confirmed at a second operation. Although 12 of the 119 patients in whom results are still good are tolerating significant regurgitation, it must be an adverse factor in their prognosis. As would be expected, mitral regurgitation proved to be an additional burden in patients with associated aortic valve disease or systemic hypertension.

It is clear that the presence of mitral regurgitation is an important factor in failure of, and deterioration after, valvotomy, and this is confirmed by Ellis and associates (33) who report regurgitation in 24 per cent of patients in relapse, in 33 per cent of failures, and in 11 per cent of those maintaining improvement, after 1,000 operations. It would appear, however, that though significant regurgitation may cause a poor result or subsequent deterioration from an initial good result, it prevents restenosis of the valve; the disappearance of mild regurgitation suggests that restenosis is occurring.

Disease of aortic and tricuspid valves.—Involvement of other valves was present in 83 of the 200 patients: the aortic alone in 45, the aortic and tricuspid in 20, and the tricuspid alone in 18; the presence of pulmonary valve disease could not be established in any.

No patient was selected for valvotomy who had aortic valve disease which was dominant or sufficiently severe to show evidence of left ventricular hypertrophy on the ECG. In 18 of the 45 patients with aortic valve disease, it was trivial and shown by a grade 1 diastolic murmur alone; of the remaining 27, 9 had aortic regurgitation alone, 8 had stenosis and regurgitation, and 10 had aortic stenosis. Only in 2 patients was the aortic stenosis considered a significant lesion; it was a definite factor in the deterioration and death of 1 patient before the introduction of aortic valvotomy, while in the other a gradient of 40 mm. Hg was found at operation and abolished by valvotomy. Functional tricuspid regurgitation is common in patients with pulmonary hypertension, heart failure, or uncontrolled atrial fibrillation, and the

diagnosis can be made if the signs disappear when hypertension is relieved by mitral valvotomy, or failure and fibrillation are treated. When tricuspid disease is considered to be of organic origin, and with minor degrees this diagnosis is not easy, the relative assessment of stenosis and regurgitation is difficult, particularly if fibrillation is present. Regurgitation is the common lesion, dominant stenosis is rare, and pure stenosis even rarer. Tricuspid disease does not contraindicate mitral valvotomy though it may limit the improvement which may be expected from a successful operation; the latter may even unmask latent disease by increasing the stroke output (62).

Excluding the 18 patients in whom a trivial diastolic murmur was the only evidence of associated valve disease, only 26 of the 65 patients with significant lesions maintained their good results through the follow-up. Although they have, as a whole, less marked aortic or tricuspid valve disease than those who deteriorated, few are without any disability and deterioration in the future is to be expected (see Fig. 2). In 15 of the 65 results after valvotomy were poor, and 24 deteriorated from initially good results; in 8 of the latter it was a major factor. While associated disease of aortic and tricuspid valves, unless very severe, is no reason for withholding surgical treatment of mitral valve disease, it indicates more widespread rheumatic heart disease and some unsatisfactory results must be expected either initially or later. Even minor abnormalities of aortic and tricuspid valves must increase the work of the heart, and long-term prognosis cannot be as good as in patients with equally good results from valvotomy who have no other abnormality.

Successful valvotomy, by increasing cardiac output, may emphasize existing signs of aortic or tricuspid valve disease, but in a few patients signs of disease, particularly tricuspid, increased gradually or developed during the follow-up; this was not correlated with any clinical evidence of rheumatic activity. It may well be that in the future we may see a higher incidence of tricuspid disease in rheumatic hearts, now that mitral valvotomy gives patients a longer span of life.

CHRONIC PULMONARY DISEASE.—One of the early criticisms of mitral valvotomy was that the histologic changes in pulmonary arterioles, first described by Parker and Weiss (64), indicated permanent pulmonary changes which would prevent any substantial benefit; it was also thought that pulmonary hypertension secondary to mitral stenosis would prove irreversible. Neither fear has been justified. After successful valvotomy, the pulmonary pressures always fall, though not usually to normal, particularly with exercise. Residual changes in the lungs after valvotomy would appear to depend on the length of time that

stenosis has been present. The electrocardiographic evidence of right ventricular hypertrophy regresses, but the degree depends on the length of time disability was present before operation (66). The interlobular lymphatic streaks or Kerley lines (50) may clear completely when the chronic pulmonary edema which they indicate is of short duration, but if they have been present for years they remain despite a good result from valvotomy. The degree to which the radiographic appearance and hemodynamic effects in the lungs are altered by mitral valvotomy is remarkable, but it is not surprising that some patients remain with chronic chest disease despite relief of mitral stenosis. They are still liable to winter bronchitis and bronchial spasm, though they distinguish this from the chronic dyspnea and orthopnea which they suffered before mitral valvotomy; emphysema also may develop. The common increase in weight after a successful valvotomy and the increased susceptibility to adverse climatic conditions and respiratory infection which a return to a normal life entails both encourage chronic chest disease. Although we have not seen cor pulmonale develop, nor any return of pulmonary hypertension, chronic chest disease must be an adverse factor in the future of these patients. This diagnosis has been made in 28 of the 200 patients. It contributed to a poor result in 3 patients, was present in 9 patients who deteriorated from good results and was thought to be a dominant factor in 4 of them, and is present in 16 patients who are still considered to be good results during the follow-up.

Systemic hypertension.—Systemic hypertension developed after mitral valvotomy in 26 patients. It was present in 9 of the 51 patients who deteriorated from good results, and in 3 it was a major factor. It also contributed to 3 of the 31 poor results. In the 14 who have maintained good results, the hypertension is well tolerated, the majority being women in whom the prognosis is so often good; none has as yet needed therapy with ganglion-blocking drugs, but deterioration is to be expected in the future in some of these patients.

Pregnancy.—Pregnancy is an exacting test of the severity of mitral stenosis. Many women experience their first symptoms during pregnancy, although permanent disability develops only some years later; some who are only slightly incapacitated before pregnancy deteriorate on becoming pregnant or die from pulmonary edema. One of the achievements of mitral valvotomy is that these patients are now able to complete a successful pregnancy; 4 patients of the 200 reviewed here, 3 with pulmonary edema, were successfully delivered after valvotomy during their pregnancy. The brighter outlook after mitral valvotomy naturally included the prospect of having children; 21 of the

158 women in the follow-up became pregnant, and 4 had a second child after valvotomy. In 2 of these 21 operative results had been poor and their condition deteriorated with pregnancy; 8 who had good operative results also deteriorated, and in 6 of them the deterioration was induced by pregnancy. All 8 were classified as good rather than excellent results and none had had a complete valvotomy. The extra demands of pregnancy clearly showed that their cardiac reserve was small and that the result of valvotomy was not so good as had first appeared. On the other hand, 11 patients were unaffected, including a woman of 39 who has successfully completed a first pregnancy 7 years after valvotomy; she has, however, always been considered an excellent result and postoperative catheterization showed a very good hemodynamic result—with an estimated valve area of 2.7 sq. cm. per square meter of body surface after a complete valvotomy.

RHEUMATIC ACTIVITY.—The incidence of Aschoff nodes found on biopsy of the left atrial appendage depends on the criteria of the pathologist who examines them, but they are found in 20 to 40 per cent of reported series. No correlation with clinical evidence of rheumatic activity or with the result of valvotomy has been found, and this has been our experience. Nor have we found that rheumatic activity is commonly apparent in adults after mitral valvotomy. Recurrent episodes of the pericardial reaction were at first mistaken for an exacerbation of rheumatism, but apart from this clear rheumatic fever occurred in only 2 patients. Both were among the 51 patients whose condition deteriorated after good results; rheumatic activity was suspected in 6 others, but in none do we think that this was directly responsible for their losing ground. Rheumatic activity was not suspected in any patient with restenosis. This could well occur by the gradual organization of platelet thrombi on a previously damaged and only partially mobilized valve, without active rheumatism. Nevertheless, both restenosis and deterioration were slightly more common in the younger than the older patients, and this may be due to rheumatic activity. Although in most cases it cannot be diagnosed, the possibility that insidious, smouldering rheumatic activity is frequently present in long-standing rheumatic heart disease cannot be ruled out. Certainly, if it is suspected, penicillin or sulfonamide prophylaxis is indicated.

MYOCARDIAL FACTOR.—The success of the surgical treatment of valvular disease has been a convincing answer to the long-held view that the state of the myocardium was the dominant factor in determining the prognosis of rheumatic heart disease. It would be wrong, however, to swing to the other extreme and to consider the muscle of no importance, either in its capacity for working against mechanical diffi-

culties or in the prognosis even when these have been surgically relieved. Of the 51 patients who deteriorated from initially good results, 8 gave no clinical evidence of restenosis, and catheterization in 6 of them did not show the hemodynamic findings of significant mitral stenosis. None of the other factors already considered was present; 5 are over 40, all are fibrillating, and none has significant pulmonary hypertension. The mitral stenosis of 1 of these 8 patients was less severe than the average, and this patient could well be classed as the myocardial type described by Harvey *et al.* (44), and Fleming and Wood (35). In these patients deterioration occurs, often initiated by the onset of atrial fibrillation, without mitral stenosis of critical severity. Although uncommon compared with the usual type in which deterioration is due directly to the severity of mitral obstruction, the same myocardial factor may well explain later deterioration in some patients whose severe stenosis has been relieved by valvotomy. It may also explain the continuance of a low resting cardiac output in many patients after successful valvotomy. A myocardial factor might also be expected in patients whose mitral stenosis has been relieved too late. Although in most patients who have had a successful operation the myocardium is an unknown factor in prognosis, it would be unwise to neglect it. Patients who have suffered disability from mitral stenosis are so impressed when they experience relief that they consider themselves normal, and act as such. The physician must assess how near or far from normal the individual patient is, and give advice accordingly. This is of no less importance and demands more clinical care and judgment than the diagnosis of restenosis.

Embolism.—Systemic embolism, particularly cerebral embolism, is one of the severe hazards of mitral stenosis. The need for valvotomy should be very seriously considered if embolism occurs, and repeated embolism is a definite indication unless mitral stenosis is absent. Of our 200 patients, 45 gave a history of embolism, multiple in 8, and at operation a clot in the left atrium was found only in 21; on the other hand, a clot was found in 18 who gave no history of embolism. It is the red, recent clot rather than the gray, old, attached clot which causes embolism. Embolism frequently occurs shortly after the onset of fibrillation, though 9 of our patients were in sinus rhythm when embolism occurred. Of the 45 patients who had emboli before valvotomy, 2 had emboli in the follow-up period. Cerebral embolism occurred at operation and caused operative deaths in the early days, and 2 patients who survived were seriously incapacitated, though the functional result was good. The technic of "washing out" clots through the atrial appendage and protecting the cerebral vessels by snares round the carotid vessels during the operative maneuvers has almost eliminated this hazard.

Systemic embolism was seen in 8 patients during the follow-up; 5 were deteriorating from good results, and 3 have maintained good results; in all, the effects of the embolism were temporary. Epilepsy following cerebral embolism in mitral stenosis is not uncommon, and occurred in 8 patients in this series, who are included in the 22 patients reported in 1957 (9).

ATRIAL FIBRILLATION.—The incidence of atrial fibrillation in mitral stenosis increases with age and also with the degree of disability. It does not, however, necessarily indicate tight or pure stenosis and is not in itself an indication for mitral valvotomy, but should weigh the balance in favor of operation if embolism occurs. There is a slightly increased operative risk in those who are fibrillating.

Fibrillation was present before operation in 41 per cent of our patients, which corresponds to other reported series (15, 38, 57, 67, 71). Bailey (4) found 48 per cent, Cooley and De Bakey (29) 49 per cent, and Ellis and Harken (32) the high figure of 54 per cent.

Of the 118 in sinus rhythm, 53 fibrillated after valvotomy. We did not think that quinidine prophylactically would prevent fibrillation, and we routinely digitalized all patients in sinus rhythm before operation. Reversion to normal rhythm occurred in 35, in 20 spontaneously. Quinidine reversion was attempted after operation or in the first year in those who had good operative results and had not been fibrillating for more than 2 years before operation; 18 failed to revert or were left to fibrillate. If fibrillation recurred after quinidine therapy it was usually accepted and controlled with digitalis. In those who deteriorated from good results, the same proportion (a third) of temporary fibrillation after operation was found as in those who maintained good results, but permanent fibrillation after operation occurred twice as often. The onset of fibrillation in those who deteriorated following a good result has been at the rate of 14 per cent a year, compared with 2 per cent in those who maintained good results. Symptomatic deterioration usually coincided with the onset of fibrillation, which was often the first indication that the degree of success had been overestimated. In contrast to most of those who deteriorated, the small number of patients who fibrillated but in whom good results were unaffected were often unaware of the onset of arrhythmia and remained symptomless without digitalis control.

REOPERATION

In only 4 of the 31 patients with poor results were second operations done, owing to the unfavorable anatomic features found at the first operation or because severe mitral regurgitation had resulted; in 3

of them the result of reoperation was also disappointing. Second operations were done in 16 of the 51 who deteriorated from good results; none had had complete valvotomies at their first operation, and in 9 restenosis had occurred; 2 died at operation, but in 14 a more satisfactory valvotomy was possible, though in only 1 was it complete. All improved, but the follow-up is too short for proper assessment of the result; 1 of the earliest has already deteriorated a second time, although the valvotomy was adequate and no restenosis has occurred; possibly, low-grade rheumatic activity and probably a myocardial factor are responsible. Renewed deterioration may well occur in the others, for restenosis may again occur in those whose valve is not fully opened and mobile. Even though our figures suggest that restenosis is less common with increasing age, deterioration may also occur by reason of the other factors we have discussed. Whatever the outcome, a second operation will have justified itself if patients enjoy a further period of increased activity, and this appears likely.

An advance in dealing with difficult valves is the use of the transventricular dilator, which has undoubtedly decreased the percentage of operative failures and made success possible in second operations. This was introduced to Great Britain by Logan in 1954 (58). Whereas in the straightforward case of mitral stenosis the commissure can be split with the finger or can be divided with an attached knife introduced through the auricle, the transventricular dilator is more efficient when the atrium presents difficulty or contains much clot, in reoperations, or in the presence of calcification. Surgeons have experienced greater security and control, using the dilator, in dealing with difficult valves.*

Selection of Patients for Mitral Valvotomy

The experience gained from following patients after mitral valvotomy is of help in the present selection of patients, and in assessing the altered prognosis after operation. Those with pure mitral stenosis, still in sinus rhythm, with no or little cardiac enlargement, without involvement of other valves, and with not too long a tolerance of disability are likely to receive more lasting benefit; evidence of pulmonary hypertension is on the whole favorable, as it is commonly associated with tight stenosis. With present technics, the chances of obtaining a complete valvotomy are good, and in such cases the danger of restenosis is not high and may never develop. Calcification of the valve

* *Editor's note.*—British authors (13a, 30a, 59) in most recent reports and some American surgeons feel that the transventricular dilator should be used at the first operation in most cases.

and associated regurgitation make a successful valvotomy less likely though not impossible, and can only be successfully dealt with by open heart surgery. Patients who are already fibrillating, with large hearts, with other valve lesions, with chronic chest disease or essential hypertension, and those in whom operation has been too long delayed are less likely to receive lasting benefit, however successful valvotomy may be. If such patients are not offered operation, a negligible operative mortality, a high proportion of successes, and a better long-term result will be achieved. This may be professionally gratifying but is not good medicine. These patients should not be denied the prospect of some improvement or amelioration of their disability, even if the benefits last only a few years, nor will they be disappointed if they are not promised too much. Such surgical results compare very favorably with operations in other diseases, in which the object is merely to increase the expectation of life.

AORTIC STENOSIS

The success of surgical treatment, first of mitral stenosis and next of pulmonary stenosis, led naturally to the surgical treatment of aortic stenosis. This has proved a more exacting problem for the surgeon, for relief of aortic stenosis without producing regurgitation is more difficult to achieve than with mitral valvotomy, and the high pressure to which the valve is subjected makes this a serious lesion compared with pulmonary regurgitation after pulmonary valvotomy. For the physician, too, selection of patients for operation has been a hard decision. In mitral stenosis, the gradual disturbance of pulmonary circulation and function usually gives adequate warning and often a liberal length of time before a critical degree of stenosis threatens life, and in Fallot's tetralogy the degree of cyanosis and polycythemia are clear indications of the severity of stenosis. In aortic stenosis, as in uncomplicated pulmonary stenosis, symptoms are rarely severe before the ventricle has failed, the prognosis is then bad and may be grave, and the optimum time for surgical treatment has passed. It is not surprising that the initial results were universally disappointing, for the surgeon was called upon to do a technically difficult operation on patients already in left ventricular failure and the physician was not happy to advise a hazardous operation until sure that the patient's future was hopeless without it. Nevertheless, there has been a steady improvement in the results even in the most severe and advanced aortic stenosis, where valvotomy is an emergency operation to relieve symptoms and prolong life. More important, the introduction of open heart surgery allows more precise relief of stenosis and limits the pos-

sibility of replacing it with the disadvantage of regurgitation. Also, left heart catheterization has provided the opportunity of correlating the signs of severity with the degree of stenosis and thus advising surgery when it is needed to prevent future deterioration and before it is too late to receive the maximum benefit.

Incidence of Severe Stenosis

Like mitral stenosis and pulmonary stenosis, aortic stenosis may, despite emphatic auscultatory signs, be a trivial lesion which may be tolerated for a long span of years and may never be a real embarrassment to the circulation. Calcific aortic stenosis in the aged, and the high age incidence in published series of aortic stenosis from hospital admissions or autopsy findings produced a clinical impression that aortic stenosis was commonly a benign lesion, particularly in the young. It may be, but often it is not, and there is increasing evidence to that effect (16, 72). Aortic stenosis of comparable severity is seen at all ages, and particularly in infancy and childhood it may cause sudden and unexpected death (11). Although any center undertaking surgical treatment will attract a selected group, we have found at Guy's Hospital that comparatively few patients can confidently be dismissed as mild and that the majority prove after assessment and investigation to have significant and usually severe stenosis. It must be emphasized that this applies to patients whose presenting symptoms are those of aortic stenosis, and excludes those with free aortic regurgitation or with dominant mitral valve disease. With combined aortic and mitral stenosis, the aortic lesion is usually less severe than as an isolated lesion, but evidence of severity may be masked by the low cardiac output and aortic valvotomy may be necessary to obtain full benefit from mitral valvotomy. In reported series in which the double operation of aortic and mitral valvotomy are included, the mortality is smaller and the clinical results are better than in aortic valvotomy alone, for they depend on the relief of the dominant mitral stenosis by the easier operation of mitral valvotomy. There is a marked male predominance in patients suffering primarily from aortic stenosis, 3.5 to 1 in the Guy's Hospital series, whereas in severe mitral stenosis there is an equally marked female predominance.

Etiology

The relative incidence of a congenital or rheumatic etiology in severe aortic stenosis is difficult to assess. There is no doubt of a congenital origin if the stenosis is subvalvar or in a valvar lesion in infancy

or childhood, and little doubt if severe stenosis develops before the age of 20. There is no doubt of a rheumatic origin if there is clear evidence of associated mitral or tricuspid disease. But in many adults with pure aortic stenosis it is difficult or impossible to decide the etiology. A history of a murmur or suspicion of heart disease in childhood is often obtained, but in many aortic disease is not diagnosed till middle age or later, usually with the onset of symptoms. Some of these patients may well have congenital lesions, as suggested by Kiloh (51) and Campbell and Kauntze (28), and bicuspid valve disease, a common and undiagnosed lesion, may well be a cause of calcified stenosis; on the other hand, the high incidence of minimal aortic lesions following rheumatic carditis would explain a delayed appearance of aortic stenosis, as suggested by Lessof (52). With either etiology, the stenosis could well remain undiagnosed until progressive calcification increased the stenosis to a critical level to produce symptoms. Nor is it easy to decide the etiology when the grossly distorted valve is examined pathologically, though the most exhaustive study, that of Karsner and Koletsky (48), favored a rheumatic origin. In 50 consecutive cases of severe stenosis operated on at Guy's Hospital (11), 20 were thought to be clearly congenital, 9 rheumatic, and in the remaining 21 the etiology could not be decided.

Percutaneous Left Ventricular Puncture

In pulmonary stenosis, measurement of the gradient across the valve by right heart catheterization provided a correlation with the ECG, so that this simple test now gives a practical and reasonably accurate measure of the severity of the obstruction. Similarly, in mitral stenosis the valve area can be estimated (39) with reasonable accuracy when checked with operative findings, and it has been possible to correlate the patient's disability with the degree of stenosis, so that the critical valve area below which deterioration is inevitable is known. Similar hemodynamic assessment in aortic stenosis, particularly needed in view of the lack of knowledge of prognosis and the late onset of symptoms, could not be achieved by right heart catheterization. Left atrial catheterization, valuable in assessing mitral valve disease, provided a method for obtaining the necessary data, but the smaller size of the left atrium and the distance from the aortic valve increased the technical difficulty. With the introduction of percutaneous left ventricular puncture (27) a more reliable and accurate method of assessing aortic valve disease, without additional hazard, became available. The gradient across the valve can be measured either by simultaneous measurement of ventricular and brachial pressures, or by catheter withdrawal; the lat-

ter maneuver is valuable in distinguishing between valvar and subvalvar stenosis. In pure stenosis, the valve area can be estimated by measuring cardiac output by dye dilution, but the presence of aortic regurgitation, by increasing the valve gradient, causes an overestimate of the severity of stenosis. It is not yet possible to determine accurately the degree of regurgitation by hemodynamic measurements, but it is possible to make an allowance for this discrepancy in calculated valve area by determining the degree of regurgitation by dye dilution as well as clinically, and by pulse pressures and the shape of the pulse waves. This method, when checked against operative findings, has proved reliable in assessing the severity of stenosis, has been valuable in excluding cases in which regurgitation is the dominant lesion or in which the part played by aortic disease in disability, usually from associated coronary disease, is in doubt, and in the diagnosis of subvalvar obstruction. Of equal importance, it provides objective evidence which can be correlated with symptoms and signs, particularly the ECG; with this accumulated knowledge it will be possible in the future to give a reasonable opinion on the prognosis of the individual patient, and thereby a reasonable decision for or against surgical treatment, on clinical evidence alone.

Symptoms and Signs of Severe Stenosis

The following observations are based on our experience at Guy's Hospital (23, 11) related to hemodynamic findings by left ventricular puncture (40). Symptoms occur late in the disease. Angina, always on effort, is common and is associated with electrocardiographic evidence of gross left ventricular hypertrophy and ischemia; if these are absent, coronary disease should be suspected. Absence of angina does not rule out severe stenosis. In younger patients, effort dyspnea was often an added symptom of advanced disease, though it did not have the same sinister meaning as in older patients in whom it was usually associated with nocturnal dyspnea and was rapidly followed by left, or later by right, ventricular failure. Paroxysmal nocturnal dyspnea was not tolerated for longer than 2 years, and recovery from frank pulmonary edema is rare. Syncope, or near syncope, without loss of consciousness, is a dangerous sign if associated with other symptoms and signs of severe stenosis, but isolated attacks may precede these by 10 to 15 years. Severe disease may be present without any signs or symptoms and with apparent good health. This is particularly so in children, in whom hemodynamic features of left ventricular failure may be found without the development of the clinical features seen in adults. The energy

and activity of the child makes greater demands on the heart and it is in such cases that sudden death may occur; this happened to 2 of our children while waiting admission for assessment, and this tragic experience is reported by others (49, 60, 63). Fatigue, with below average stature may be useful pointers to the severity of the disease in children.

Reliance on signs of severity is emphasized by the late onset or absence of symptoms. The slowly rising pulse with anacrotic notch may be absent in the young and in subvalvar stenosis. A small pulse pressure indicates pure stenosis but is not a constant finding, particularly in older patients. A wide pulse pressure or carotid pulsation suggests significant regurgitation or rigid atheromatous great vessels. Except in heart failure, the systolic murmur is sufficiently intense to produce a thrill, though the maximum intensity may be well above the valve site, or toward the apex in subvalvar lesions; conversely, a thrill may be found with insignificant stenosis, particularly with calcified valves. A diastolic murmur of grade 3/6, or 3 out of 6, intensity is a reliable sign of significant regurgitation, particularly if supported by an above average pulse pressure, a rapid fall of pulse after a prolonged upstroke, and radiographic evidence. A large heart is not common in severe, uncomplicated stenosis, though the rounded contour of left ventricular hypertrophy is characteristic and constant. Prominence of the first part of the aorta is seen in valvar lesions, but may be absent in subvalvar ones. Marked cardiac enlargement is seen when there is involvement of other valves, heart failure, or significant regurgitation, which is confirmed by radiography in the left oblique position; this shows an elongated left ventricular contour with wide dynamic excursions transmitted to the aortic arch. Valve calcification is an important finding, and must be sought by fluoroscopy, by heavily exposed chest x-rays, or by tomography; its absence in an adult means that the lesion may be subvalvar or that functional stenosis is present (22). The youngest patient seen with calcification was a woman of 24, and the oldest without it a woman of 27. Left atrial enlargement may indicate associated mitral valve disease, but is seen in pure aortic stenosis with left ventricular failure; radiographic evidence of pulmonary venous congestion may then be seen, but interlobular lymphatic streaks (Kerley lines), so common in mitral stenosis, are rare, presumably due to the short time that left ventricular failure can be tolerated.

Electrocardiogram.—The physical signs help mainly in the diagnosis of pure aortic stenosis. It is the ECG which is of most help in assessing the severity of the disease. We have seen no ECG without evidence of left ventricular hypertrophy in which the mean gradient is

below 50 mm. Hg or in which the valve area in pure stenosis is above 0.7 sq. cm. per square meter of body surface, the figures now accepted as indicating critical stenosis. As would be expected, with associated regurgitation, abnormal ECGs are found with a high gradient and a larger valve area. Ventricular activation time is commonly prolonged and left bundle-branch block may develop. We have seen this in a woman of 24 who had had a normal ECG 4 years earlier. Inversion of T waves may be over 8 mm. in those with symptoms; if these changes are not marked in adults with marked disability or failure, coronary disease must be strongly suspected. Severe T wave changes may, however, be present without symptoms, particularly in the young, and we have found up to 20 mm. inversion in subvalvar stenosis. Although a rough correlation existed between T wave changes and disability in valvar stenosis, it is not surprising that there was little correlation with valve area, estimated preoperatively or at operation, since these changes must be related to the length of time that the ventricle has had to work against a critical degree of stenosis. We have found very severe stenosis in children in whom T wave changes had not yet developed, although the QRS voltage indicated hypertrophy. There must be a critical valve size below which future deterioration is inevitable, and it may well be that this could be present with a normal ECG; but, on the present evidence, we think that every patient with T wave abnormality is already deteriorating. Physical activity must influence the speed with which deterioration may occur, so that particularly careful observation and electrocardiographic scrutiny are essential, particularly in children who are by nature active. Assessment of valve area by catheterization is a justifiable procedure, especially in children, unless it is certain that the stenosis is mild. This does not mean that all patients are in immediate need of surgical treatment, but it will help in the prognosis and the advice given to the individual patient, and the accumulation of such data, linked with clinical observation and electrocardiographic evidence will add greatly to our knowledge of the disease.

Functional Obstruction of Left Ventricle

Functional subvalvar, or infundibular, stenosis in the right ventricle (19, 21) is well recognized, but a similar condition may occur in the left ventricle. With clinical evidence typical of aortic stenosis and a large gradient between left ventricle and aorta, the obstruction is muscular, and no operable valvar or subvalvar stenosis is found (14, 22). The importance of recognizing these cases is obvious. It is also thought that functional muscular obstruction occurs secondary to organic aortic

stenosis, as has been clearly shown in pulmonary valve stenosis (45–47). This would explain why good results are obtained after aortic valvotomy when the gradient at operation is not greatly lowered; in 1 of our patients who had an excellent clinical result, left ventricular puncture 3 years after operation showed a gradient of 30 mm. Hg and an estimated valve size of 3.3 sq. cm. per square meter of body surface, though the postoperative gradient immediately after operation was 108 mm.

Surgical Treatment

Apart from an isolated report by Tuffier (70) in 1913, the first surgical approaches were by Smithy (68), himself a victim of the disease, and by Brock (17), whose first operation was in 1947. In an early report, Bailey and colleagues (6) noted that regurgitation was apt to occur when the cutting valvotome was used and recommended a splitting of the valve with an expanding dilator. After wide experience with the transventricular approach to the valve, they rejected it in favor of the transaortic operation (7); this was also strongly advocated by Harken (41), and has been generally favored by American surgeons (34, 54). Glover (36), on the other hand, used the transventricular route, as have British surgeons (58), and Brock (23) made a strong case for its comparative safety, as shown by his own results.

The reports on closed operations in the literature show that after a high initial mortality satisfactory results are obtainable, though the mortality remains higher than with mitral valvotomy, and regurgitation is difficult to avoid. Glover (36) reported 7 deaths in 22 operations, 6 combined with mitral valvotomy, but 4 years later, in the last 41 operations, the mortality was 4.9 per cent, with 34 successes in the 37 survivors (37). Marquis and Logan (61) emphasized the dangers of regurgitation after valvotomy in an excellent report with full clinical details. Harken *et al.* (43) reported a 12 per cent mortality in 100 transaortic operations on calcified valves, but there were only 5 deaths in the last 60 operations.

The difficulties of successfully relieving stenosis in the grossly distorted valves which are usually encountered, without producing regurgitation, naturally emphasized the need for surgery under direct vision, and cardiac surgeons were approaching this generally desirable and logical objective during this period. Lewis *et al.* (53) reported 3 operations under hypothermia; this was tried by others, but the operating time available with this technic was too short, and cooling of the strained and often already defeated ventricle readily produced fibrillation in our experience at Guy's Hospital (11). Operation with the use

of a by-pass was clearly necessary. Lillehei *et al.* (55) first reported success in a single case with complete by-pass and retrograde coronary perfusion, and 2 years later they reported on 8 operations, 4 on calcified valves, with 3 deaths (56). This is undoubtedly the operation of the future; it is already being widely used, though there are as yet no published reports of any large series.

However, there is still a place for the closed operation, particularly in older patients who are not seen until they are already in immediate danger with left ventricular or even congestive failure. In 31 consecutive operations at Guy's Hospital in this older age group with calcified valves, 13 of whom had already been in heart failure, the results were as follows: only 4 operative deaths; serious regurgitation in 2 patients only; good relief of stenosis, confirmed by hemodynamic measurement and a follow-up of 9 months to 3½ years, in 16. We think that these results in a group with such advanced disease and with so grave a prognosis are a clear justification for this operation. Furthermore, good results were obtained in all patients with subvalvar stenosis by this method; it has therefore much to recommend it, particularly in the stage where the open procedure itself constitutes a definite hazard (11).

The progress of surgical treatment is shown by our experience. The initial results were disappointing. Although it is never fair or wise to assess the future of cardiac surgery in a pioneer period, we reported our early results to emphasize that aortic valvotomy was a more difficult problem than mitral valvotomy, in which good results had been obtained from the start. In the first 16 patients, there were 6 operative deaths and only 5 satisfactory results (8). In the next 50 operations, still in severe and advanced disease, there were 9 operative deaths, good results were obtained in 23, and excellent results in 5, when critically assessed with hemodynamic data and a follow-up period of up to 3½ years (11). Brock's (25) figures for operations done both at Guy's Hospital and the Brompton Hospital up to March, 1959 are: for valvar stenosis, 19 open valvotomies with 6 deaths, and 127 transventricular closed valvotomies with 19 deaths, and in the last 100 operations by this route 7 deaths; for subvalvar stenosis, 4 open operations with 2 deaths, and 14 closed transventricular operations with no deaths. Success, not yet reported, is now being consistently obtained by open heart surgery using total by-pass.

I would summarize the present position thus: Aortic stenosis, whether congenital or acquired, whether valvar or subvalvar, is a serious and rapidly fatal disease at all ages if the degree of stenosis is critical. When that is so, medical treatment is at best palliative and not long effective. The need for surgical relief of stenosis is therefore clear. In

advanced disease the decision to operate is not difficult as the prognosis without operation is grave, and even incomplete relief of stenosis relieves symptoms and prolongs life. The closed transventricular approach is still a good operation in subaortic stenosis and as an emergency operation in advanced disease with gross valvar calcification. In younger patients with stenosis when calcification is slight or absent, open heart surgery by pump-oxygenator promises good relief of stenosis without producing regurgitation. With increasing experience, improved results and a lowered mortality will make it possible to select patients at an earlier stage in the disease when they can obtain the maximum benefit. In the meantime, correlation of hemodynamic data with careful clinical observation should determine the critical degree of stenosis which makes surgical treatment essential.

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Newer Diagnostic Technics in Congenital Heart Disease

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FIFTEEN years ago the physician's responsibility to his patient with congenital heart disease could generally be discharged with relative ease. It was only necessary for him to establish that a congenital cardiovascular anomaly was present and to categorize broadly the nature of the lesion. A specific anatomic diagnosis was unnecessary unless the presence of one of the few extracardiac lesions amenable to surgical treatment was suspected. Since in most patients specific surgical correction was impossible, treatment could be directed only at the symptoms and complications as they appeared and progressed in inevitable sequence.

Today, almost every patient with congenital heart disease is a potential candidate for operation. However, the risks and results of operation vary widely among the different anatomic lesions and are constantly changing as improvements are made in surgical technic and postoperative care. Therefore, the physician's primary responsibility today is to define, as precisely as possible, the anatomy of the lesion and the extent of its detrimental effects upon the circulation. Only when this has been accomplished can he undertake the task of advising the patient or his family about the desirability of operation and the optimum time for it. Precise and complete preoperative characterization of the defect is also mandatory for intelligent planning of the operation. The surgeon must know, for example, the optimal site for the thoracotomy and that the special technics of hypothermia and extracorporeal circulation may be needed and should be available.

In the diagnosis of congenital cardiovascular malformations, as in

all medicine, the clinical examination is of paramount importance. On the basis of the history, physical examination, x-rays and ECG, the need and course of special investigative methods can be charted. Some of these studies may be time consuming, expensive, and even entail significant risk. However, when used in the appropriate patient by an experienced diagnostic team, the benefit from the information derived usually far outweighs all other considerations. Not all of the technics described below are ever necessary in any one patient; the availability of most of them and their judicious use for a particular problem will usually assure a correct anatomic and physiologic diagnosis.

RIGHT HEART CATHETERIZATION

Right heart catheterization is the most important single physiologic technic for the diagnostic study of patients with congenital heart disease. In addition to providing measurements of pressures and oxygen saturation within the right heart and pulmonary circulation, it permits application of the newer, more specialized diagnostic methods, including the foreign gas technics, indicator-dilution curves, selective angiocardiography, intracardiac phonocardiography, and intracardiac electrocardiography.

Catheter Positions

The course of the catheter within the heart and great vessels gives important diagnostic information. For example, the presence of an interatrial communication can be definitely established by passing the catheter across the defect. In our experience, when the procedure is carried out from the saphenous vein, inability to pass the catheter into the left atrium effectively rules out the presence of an atrial septal defect. When the point of the catheter's crossover into the left atrium is relatively low in the cardiac silhouette, the presence of a persistent ostium primum defect is suggested (13). In Ebstein's anomaly, the catheter characteristically coils in a greatly enlarged right atrium and crosses the tricuspid orifice well to the left of the midline (14). When a left-to-right shunt into the pulmonary artery is present, the passage of the catheter from the pulmonary artery into the ascending aorta permits the recognition of an aortic septal defect. Occasionally, in such patients, the catheter can then be passed in a retrograde fashion to the aortic valve (77). When the catheter traverses a patent ductus arteriosus it generally passes into the descending rather than the ascending aorta.

The use of a single- or double-lumen catheter with an inflatable

balloon may be of value in estimating the actual size of an atrial septal defect. After the catheter is passed across the defect the balloon is progressively filled with a radiopaque substance until it cannot be withdrawn into the right atrium. An x-ray taken with the balloon temporarily wedged in the defect indicates the size of the interatrial communication (12, 99, 187). If the significantly distended balloon can pass into the right atrium from the left, a nonshunting patent foramen ovale may be excluded; if it passes across the mitral orifice into the left ventricle, an associated mitral stenosis (Lutembacher's syndrome) is not present (99). This technic will only indicate the least dimension of a single interatrial defect or, when multiple communications are present, the size of the one in which the balloon is engaged.

Intracardiac Pressure Pulses

The pressure pulses recorded from within the cardiac chambers and great vessels give not only important diagnostic information but in many instances are basic for the assessment of the physiological consequences of the lesion. Unfortunately, numerous artifacts distort the true pressure pulse. Practically, perhaps the most important of these is produced by the catheter motion induced by cardiac contraction. Wood and associates (202) have carried out both *in vivo* and *in vitro* studies of the dynamic response characteristics of cardiac catheters. They observed that catheter-manometer systems with a uniform dynamic response to 5 to 10 cycles per second and a sharp cut-off in sensitivity at higher frequencies yielded recordings with the least evidence of distortion.

Analysis of the atrial pressure pulses often furnishes useful diagnostic information. In pulmonic stenosis, the right atrial *a* wave is prominent (99), and in those patients with greatly elevated right ventricular pressures a positive *x* wave, i.e., an upward deflection in midsystole between the *c* and *v* waves often occurs (166). Similarly, a tall *a* wave is characteristic of tricuspid atresia (99) and of Ebstein's anomaly (14). Hemodynamic evidence of tricuspid regurgitation has also been noted in the latter malformation (14, 166). In contrast, in patients with atrial septal defect the right atrial *x* descent and *v* wave *are particularly prominent. The former is related to the vigorous* descent of the base produced by the hyperdynamic right ventricle while the latter results from overfilling of the right atrium (88, 153). In a series of 27 patients with atrial septal defect studied by Haroutunian and co-workers the ratio of *a* to *v* was 1.2 or less, and lower than in normal subjects (19) or in patients with ventricular septal defect

(88). When pulmonary hypertension is associated with atrial septal defect, the *a* wave becomes taller. Many of the characteristics of the atrial pressure pulse may also be detected by indirect recording or careful observation of the jugular venous pulse.

Sequential pressure recordings of both atrial pressure pulses are of value in the differentiation of atrial septal defect from nonshunting patent foramen ovale; only a small interatrial pressure gradient occurs in atrial septal defect (165), but a much larger gradient is observed when both atrial pressures are measured simultaneously (19) or sequentially (165) in the presence of a nonshunting foramen ovale.

When there is obstruction to right ventricular outflow and the interventricular septum is intact, right ventricular contraction is more isometric than normal. The right ventricular pressure pulse is symmetrically rounded or peaked (89, 98), and the summit of the pressure is reached late in systole. In contrast, when an associated ventricular septal defect is present the right ventricular pressure pulse exhibits the normal ejection plateau (98). In patients with marked pulmonary hypertension, there is an upward slope of the right ventricular pressure pulse during systole (89). As the catheter is withdrawn across a stenotic pulmonary orifice, a negative deflection can be recorded in systole due to the Venturi or "sucking" effect produced by the high velocity of the blood flow (170). In patients with ventricular septal defect, the administration of pressor amines may be of diagnostic value, since a significant rise in pulmonary artery pressure occurs synchronously with the elevation of systemic arterial pressure (185).

Postvalvular pulmonic stenosis, a recently-recognized malformation, may be diagnosed by noting a pressure gradient within the pulmonary artery (60, 149, 199). When the tip of the catheter is wedged in a peripheral pulmonary artery, free communication is established between the lumen of the catheter and the pulmonary capillary–venous bed. In the absence of an obstructing lesion between the pulmonary capillary bed and the left atrium, this makes possible an estimation of left atrial pressure. In congenital mitral stenosis (17, 65) and cor triatriatum (163), the pulmonary artery wedge pressure and the pulmonary artery pressure are elevated, a finding of considerable diagnostic value. In congenital mitral insufficiency, a tall *v* wave in the pulmonary artery wedge pressure pulse has been observed (99).

One of the most important recent developments in cardiac catheterization has been its use in infants (210) and young children, even when they are severely disabled or in heart failure (174). In many centers, cardiovascular diagnosis in such patients is now approached in a more aggressive manner than heretofore. Almost no patients are con-

sidered "too sick" to catheterize (98), and a substantial number of infants have been saved by early diagnosis and appropriate surgical treatment. The use of a "lytic cocktail" consisting of Thorazine, Demerol, and Phenergan for sedation, has greatly simplified diagnostic studies in children and in many has eliminated the need for general anesthesia (98).

The recent introduction of the fluoroscopic image amplifier significantly decreases the radiation received by both the patient and physician during cardiac catheterization and even permits the procedure to be carried out in a lighted room (211). Rudolph and Cayler (155) have emphasized the importance and have described a method for the measurement of oxygen consumption at the time of cardiac catheterization in young children, a technic neglected in most laboratories.

LEFT HEART CATHETERIZATION

Several technics have recently been developed for measuring left heart pressures. In transbronchial left heart catheterization (134, 137), a bronchoscope is first passed to the level of the carina; a needle is then inserted through the left main bronchus and into the left atrium which lies in close relation to it. After left atrial pressure is measured, a thin plastic catheter may be advanced through the needle into the left atrium, across the mitral valve, into the left ventricle, and frequently across the aortic valve into the ascending aorta. The bronchoscope and needle may be removed with the catheter remaining in the left heart and hemodynamic measurements continued without the stress of bronchoscopy (134). The chief advantage of this method appears to be its distinct safety as compared to other technics; the major disadvantages are that the services of a skilled endoscopist are required and that the patient is subjected to the stress and discomfort of bronchoscopy. Furthermore, bronchoscopy is undesirable and difficult in children since general anesthesia is required and the bronchi are relatively small.

In the posterior transthoracic technic, a needle is introduced into the left atrium, generally under fluoroscopic guidance, through a right paravertebral approach. A plastic catheter passed through this needle then permits measurement of left ventricular and aortic pressures. The chief advantage of this method is its technical simplicity and absence of discomfort for the patient. However, the development of pneumothorax, hemothorax, and cardiac tamponade have been occasional complications (31).

A more recently introduced method, particularly suited for the

study of children and of patients of all ages with aortic valvular disease, is percutaneous puncture of the left ventricle through the anterior chest wall (31, 66). This method, however, does not permit measurement of left atrial pressure.

The ease with which a cardiac catheter, introduced from the saphenous vein, can be directed across an atrial septal defect suggested the transseptal approach to left heart catheterization. After isolation of the saphenous vein a standard catheter may be introduced and complete right heart catheterization carried out. A shortened no. 8 Lehman catheter is then passed into the right atrium and a specially constructed, curved, 17-gauge needle is inserted into it. The tip of the catheter, still enclosing the needle point, is positioned fluoroscopically to lie against the interatrial septum near the fossa ovalis. Often the catheter tip can be engaged beneath the superior rim of the fossa. The needle is then pushed from the catheter, punctures the septum and enters the left atrium. The left ventricle, and occasionally the aorta, may be catheterized by a fine polyethylene catheter passed through the needle. The transseptal route has the distinct advantage of allowing combined right and left heart catheterizations to be carried out with the patient under basal conditions. The procedure results in no more discomfort than that accompanying any right heart catheterization and appears to be benign. The technic has been found particularly suitable in children and prolonged observations of left heart pressure are easily obtained (154 a, b, c).

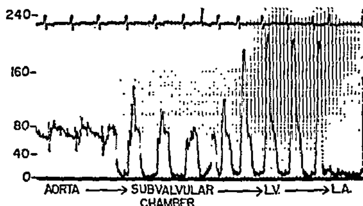


FIG. 1—Pressure tracing recorded in 16 year old boy with congenital subvalvular aortic stenosis; diagnosis was subsequently confirmed at open operation. Transbronchial catheter was withdrawn across aortic valve and then across subvalvular membrane into main left ventricular cavity (L.V.) and left atrium (L.A.) (136).

An important use of left heart pressure measurements has been detection of the presence of congenital aortic stenosis and determination of the severity of the obstruction to left ventricular outflow (135, 136). Measurement of the gradient across the aortic valve may be combined with the simultaneous determination of cardiac output by the indicator-dilution technic (134). Calculation of the effective orifice size by the Gorlin formula (82) is then possible and permits rational selection of patients for aortic valve surgery. The site of obstruction to left ventricular outflow may be localized to the aortic valve, or the supravalvular or subvalvular region by the continuous recording of pressure as the catheter is withdrawn from the aorta to the left ventricle (29c, 135, 138a, 138b) (Fig. 1).

BLOOD OXYGEN ANALYSES

The sampling of blood from the venae cavae, the chambers of the right heart, and the pulmonary artery, and the demonstration of a rise in the oxygen content as the catheter is advanced, has been the standard method for the characterization of left-to-right shunts (49, 53). The development of a practical whole blood oximeter by Wood (85, 201) has greatly simplified the application of this technic since only small quantities of blood are required and the analysis is almost instantaneous. Oximetry is based on the fact that red light (640 μ) is transmitted by oxyhemoglobin but absorbed by reduced hemoglobin. However, infrared light (800 μ) is transmitted identically by both forms of hemoglobin. The saturation of the blood is derived by relating the light transmission at these two wave lengths. Oximetry may also be applied to the heat-flushed ear and permits estimation of the arterial oxygen saturation without arterial puncture (145, 200). While ear oximetry is not a precise technic, it may be of considerable value in the study of infants and young children with congenital heart disease in whom arterial cannulation is difficult. In such patients, the effects of posture, exercise, and oxygen breathing may be determined. The ear oximeter is also useful for estimating arterial oxygen saturation in children who are questionably cyanotic (98), as well as in the differentiation of cyanosis due to right-to-left cardiac shunts from that seen in patients with pulmonary or acquired heart disease. During combined exertion and oxygen administration, oxygen saturation falls in the first group of patients, but rises in the latter (206). Since the Valsalva maneuver results in the reversal of a small or moderate left-to-right interatrial shunt (118), the ear oximeter may be employed in a simple test for atrial septal defect.

Of considerable interest is the recent development of a cuvette oximeter for use with hemolyzed blood (154). A light source and small photocell have also been placed at the tip of a cardiac catheter and may prove useful for detecting cardiac shunts without withdrawing blood (8).

The determination of arterial oxygen saturation is important in patent ductus arteriosus with right-to-left shunting; the oxygen content of blood obtained from the femoral artery is less than that obtained from the right brachial artery (35). However, a similar observation has also been made in a patient with an aorticopulmonary window (67). Recently, Samet *et al.* (157) demonstrated the diagnostic value of the arterial oxygen saturation when different gas mixtures were delivered to the two lungs by means of differential bronchospirometry in a patient with anomalous pulmonary venous drainage. The arterial oxygen saturation remained unchanged when pure nitrogen was administered to the lung with the anomalously draining veins, but fell abruptly when it was given to the lung with normal venous drainage.

In many laboratories, the oxygen method for detecting left-to-right shunts yields inconclusive results in a significant number of patients (98, 135, 160). The use of the oxygen method for the quantification of left-to-right shunts is fraught with many inaccuracies which are well recognized. It may be of interest to examine the reasons for the limitations of the oxygen method. Since the oxygen content of right heart blood is a function of the cardiac output and of the total peripheral oxygen consumption, it varies markedly among different subjects and in the same subject at different times. Therefore, it is necessary to compare the oxygen content of blood obtained from the chamber proximal to the entry of the suspected shunt to that obtained from the chamber distal to it. During the time required for positioning the catheter and withdrawing several blood samples in each chamber, changes in the patient's total oxygen consumption and cardiac output may obscure the changes produced by a shunt.

When the oxygen content of blood samples obtained from two different chambers is compared, it is assumed that these samples are entirely representative of the blood within that chamber. However, it has been demonstrated that the blood in the venae cavae and right atrium is incompletely mixed. Laminar flow and streaming occur in these areas, leading to difficulties in the diagnosis of left-to-right shunts, particularly those at the atrial level (49, 54, 135, 168, 192). For example, the sampling of a stream of well-oxygenated renal venous blood in the inferior vena cava may mask an atrial septal defect.

In some patients, the catheter cannot be passed into the inferior vena cava. Since it has been conclusively demonstrated that the oxygen content of superior caval blood is generally less than that of inferior caval blood (98, 135), a comparison of superior caval and right atrial blood could lead to the false diagnosis of an atrial septal defect.

The criteria for a "significant" oxygen step-up vary considerably among different laboratories. Thus, a difference of 2.5 volumes per cent in oxygen content between venae cavae and right atrium is required for the diagnosis of a left-to-right shunt at the atrial level in one laboratory (127). On the other hand, Barrat-Boyes and Wood (7) have achieved far greater sensitivity with the oxygen method by repeatedly withdrawing pairs of blood samples from two chambers in rapid succession and analyzing these in the cuvet oximeter.

FOREIGN GAS TECHNICS

Inhalation Technics

In view of the aforementioned limitations of the oxygen method, the use of an inert foreign gas for the detection of left-to-right cardiac shunts was suggested by Callaway and this technic has received extensive clinical application at the National Heart Institute (28, 131, 135, 159, 160, 161). During the first minute or two of inhalation of an inert foreign gas, such as nitrous oxide (N_2O) or radioactive krypton (Kr^{85}), its concentration in blood in the left side of the heart and the peripheral arteries rises sharply, then levels off. Since these gases are quite soluble in the body's tissues, their concentration in the systemic veins rises much more slowly. Hence, in the absence of a left-to-right shunt, the content of N_2O or Kr^{85} in the right heart or pulmonary artery blood constitutes a small and relatively constant percentage of the arterial content.

However, in the presence of a left-to-right shunt, blood from the left side of the heart, rich in foreign gas, is shunted across to the right side of the heart, thereby elevating the gas content of right heart blood and the ratio of the concentration of right heart to arterial N_2O or Kr^{85}. Determination of the presence or absence of a shunt may therefore be based simply on this ratio, and requires only two blood samples. The systemic and pulmonary arterial N_2O contents during the 10 minutes of inhalation in a patient without a cardiac shunt are illustrated in Figure 2. The marked difference in N_2O content between systemic and pulmonary arterial blood during the first 2 minutes of inhalation is apparent.

The results of 150 N_2O tests performed in 98 patients are illustrated in Figure 3; 15 per cent N_2O and 21 per cent O_2 in N_2 were inhaled for 30 seconds, and arterial and right heart samples were drawn at a constant rate between seconds 10 and 30 of inhalation. In all 96 tests performed in patients without shunts, the level of N_2O in the right side of the heart or pulmonary artery was less than 15 per cent of the arterial level, and in 91 of the 96 tests it was less than 10 per cent. In

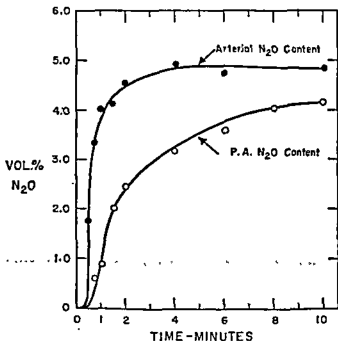


FIG. 2.—N_2O levels in femoral artery and pulmonary artery (P.A.) of patient without a left-to-right shunt who inhaled 15 per cent N_2O for 10 minutes; large arteriovenous difference is present during first minute of inhalation (135).

the 72 N_2O tests performed in 35 patients with left-to-right shunts, with one exception, the N_2O content of blood sampled in or distal to the chamber receiving the shunt exceeded 15 per cent of the arterial N_2O content. Thus, with this one exception, the presence or absence of a shunt was correctly indicated.

The foreign gas technics may also be employed in the quantification of left-to-right shunts. The N_2O content of blood obtained distal to the entry of a left-to-right shunt reflects the mixing of venous blood, low in N_2O content, with shunted blood rich in N_2O content. The proportion of pulmonary artery blood derived from shunted blood may then

be calculated from a consideration of the gas contents in venous blood, in shunted blood, and in the pulmonary arterial blood. There is little variation in the concentration of gas in venous blood proximal to any shunt; it has been found to be 6 ±6 per cent of the arterial level (159). The N_2O content of shunted blood may be considered to be identical with that of arterial blood. The ratio of pulmonary to sys-

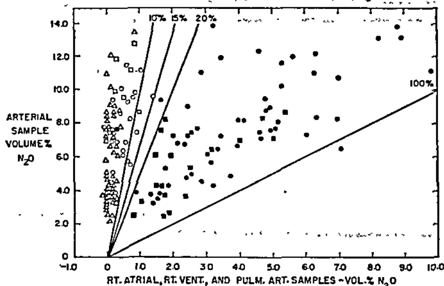


FIG. 3.—Relation between right heart and peripheral arterial N_2O levels (159). Δ, adults, rheumatic; ■, □ adults, nonrheumatic; ●, ○ children; solid symbols, patients proved to have left-to-right shunts; open symbols, patients proved not to have left-to-right shunts.

temic flow can then be calculated from the following formula (42, 63, 159):

$$\frac{\text{Pulmonary flow}}{\text{Systemic flow}} = \frac{100\% - 6\%}{100\% - P.A./A.\ (\%)}$$

where *P.A./A.* represents the N_2O or Kr^{85} test result in the pulmonary artery.

In order to determine the validity of this formula, both the total pulmonary blood flow as well as blood flow through an artificial left-to-right shunt were measured directly in a group of dogs by means of electromagnetic flowmeters (162). N_2O tests were then performed while shunts of various magnitudes were functioning. No systematic difference between the flow ratios determined by the two methods was observed; the coefficient of correlation was 0.96.

In view of the necessity for analyzing N_2O in the Van Slyke manometric apparatus, it was thought that other inert gases might behave in a similar manner, but permit easier and faster analysis (42, 158). Kr^{85} had been evaluated experimentally and found as satisfactory as N_2O in the diagnosis of left-to-right shunts. Arterial and right heart blood samples drawn during seconds 10 to 30 of Kr^{85} inhalation may be analyzed simply by inserting them into a continuous gas-flow Geiger-Müller tube capable of counting beta emissions. The results with the clinical use of Kr^{85} are essentially identical to those obtained with N_2O (160, 161).

The oxygen and Kr^{85} methods were compared in a group of 54 patients in whom both technics were applied at the same right heart catheterization (160). Among the 32 patients with proved left-to-right shunts, there were 6 with oxygen step-ups less than 1.0 volume per cent into the chamber receiving the shunt. In the group of 22 patients without a shunt there was one with an oxygen increase greater than 1.0 volume per cent. The oxygen method thus would have provided an incorrect diagnosis in 7 of the 54 patients. There were no errors with the Kr^{85} method; in all 22 patients proved not to have shunts, the Kr^{85} test was less than 15 per cent. It exceeded 15 per cent in all 32 patients with proved left-to-right shunts.

Injection Technics

The relatively poor solubility of Kr^{85} in blood suggested a totally different approach to the study of patients with cardiac or intrapulmonary shunts. When Kr^{85}, dissolved in saline, is injected into a peripheral vein or into the right side of the heart, that portion which passes through capillaries perfusing normally ventilated alveoli comes out of solution and immediately appears in the expired gas. Clearance by the lungs is approximately 95 per cent complete during one circulation (44) and, therefore, the levels of Kr^{85} in arterial blood are only slightly above background following right heart or intravenous injections in the absence of a right-to-left shunt. However, when the injection is made proximal to the origin of a right-to-left shunt, that portion of the Kr^{85} which by-passes the pulmonary capillary bed appears in the arterial blood and leads to an elevated arterial Kr^{85} level. The validity of this concept has recently been demonstrated in a group of dogs with experimentally produced right-to-left shunts (113) as well as in patients (21, 28, 112) with congenital heart disease and right-to-left shunts.

Immediately after injected Kr^{85} arrives in the pulmonary artery it

appears in expired gas, where it may be readily detected by means of an end-window Geiger-Müller tube inserted directly into the expiratory gas line, and its concentration recorded continuously with a count rate meter and direct writing recorder (21, 28, 111, 112). This affords a relatively simple method for detecting the presence of left-to-right cardiac shunts as well as for localizing their site of origin. Kr^{85} which is injected into the left side of the heart proximal to the origin of a left-to-right shunt appears in the expired gas in less than 5 seconds, but when it is injected into the left side of the heart or aorta distal to the origin of a left-to-right shunt it must first traverse the systemic circulation before reaching the pulmonary circulation and its appearance in the expired gas is delayed, and generally longer than 10 seconds.

This method appears to be sensitive enough to detect even the smallest left-to-right shunts and to be as sensitive as any of the dye dilution technics. Only one catheter need be inserted into the heart; no blood samples are required; the results of the study are available instantaneously; the instrumentation required is not complicated; and the risk of the catheterization does not appear to be increased.

INDICATOR-DILUTION TECHNICS

At the present time, indicator-dilution curves constitute one of the most important diagnostic technics in the recognition and localization of cardiac shunts. One of the first indicators employed in the study of patients with congenital heart disease was ether; the intravenous injection of 0.2 to 0.5 ml. may be used to detect right-to-left cardiac shunts. Benenson and Hitzig (9) demonstrated in 1938 that in the absence of a right-to-left shunt this substance is immediately and entirely eliminated in expired air; if it reaches the systemic circulation through a central circulatory communication the patient experiences paresthesias over the face, scalp, and chest (9, 98, 150). The selective injection of ether into the right atrium, right ventricle and pulmonary artery thus permits localization of the site of origin of right-to-left shunts (58). It is of interest that in 1941 Prinzmetal calculated the magnitude of right-to-left cardiac shunts by varying the doses of two indicators, ether and saccharin (150). The appearance time of decholin in the tongue following its injection into the right ventricle has also been employed in the detection of right-to-left shunts at the ventricular level (126).

The measurements of circulation time by these methods suffer from depending on a subjective response requiring the patients cooperation. For this reason, Ziegler (209), Lasser *et al.* (100), and Gordon *et al.*

(81) utilized indicators permitting more objective detection. These investigators demonstrated that when fluorescein (209) or Evan's blue dye (81, 100) is injected into the right ventricle it appears earlier in the systemic circulation of patients with the tetralogy of Fallot than in those with pulmonic stenosis and patent foramen ovale. The development of oximeters and densitometers for the continuous registration of the concentration of colored indicators (71, 76, 129, 164, 183, 201) in the blood stream, i.e., the recording of dye-dilution curves, has greatly extended the applications and diagnostic value of circulation time measurements. Wood, Swan, and their collaborators at the Mayo Clinic have pioneered in the development, application, and perfection of these important, entirely safe, technics.

Right-to-Left Shunts

After an indicator is suddenly injected into the vascular bed, it is dispersed in and follows the normal and abnormal pathways traversed by the blood (204). After injection into the right heart proximal to the origin of a right-to-left shunt, an indicator follows two circulatory paths. A portion takes the normal route through the pulmonary circulation, thence through the left side of the heart and into the systemic arterial bed; this fraction of the indicator produces the normal component of the resultant dilution curve. The remainder of the indicator courses with the blood through its abnormal circulatory path, i.e., it is shunted from the right to the left side of the heart, by-passes the pulmonary circulation, and appears at an abnormally early time in the systemic arteries. This fraction of the dye is responsible for the abnormal component of the dilution curve, i.e., it results in an abnormally early appearance time and a peak which precedes the normal component of the curve. Either a double-peaked contour or an early appearance time followed by an abrupt change in the slope of the ascending limb results from the difference in length of the two circulatory paths traversed by the indicator. The selective injection of indicator dye into the right atrium, right ventricle, and pulmonary artery makes possible the precise localization of the origin of a right-to-left shunt (180, 182, 206) (Plate 1). For example, in a patient with pulmonary stenosis with a right-to-left shunt through a patent foramen ovale, injection into the right atrium results in an abnormal dilution curve, and a normal curve follows right ventricular injection. In contrast, in a patient with the tetralogy of Fallot, dye injections into both the right atrium and right ventricle result in abnormal curves with early appearance times. In such a patient, the appearance time after

injection into the pulmonary artery is normal. The injection of indicator into a peripheral vein serves as a valuable screening test in the study of patients with cyanosis of central origin (206). The abnormal curves just described are obtained in patients in whom the cyanosis is secondary to a right-to-left cardiac shunt, but in patients with intrapulmonary shunting, i.e., with well-perfused but inadequately ventilated pulmonary areas, normally shaped dilution curves result. In the former patients the presence of the right-to-left shunt shortens the circulatory path while in the latter it does not.

The differential diagnosis between tetralogy of Fallot and pulmonary atresia may be facilitated by recording arterial dilution curves after injection of indicator dye into both the right ventricle and the aorta. The curves are identical when the entire right ventricular discharge is into the aorta, as in pulmonary atresia (196). Indicator-dilution curves have also been found to be of value in determining whether the aorta or the pulmonary artery has been entered at the time of catheterization (147).

Left-to-Right Shunts

When an indicator is injected into a peripheral vein, right side of the heart, or the pulmonary artery of a patient with a left-to-right cardiac shunt, it is dispersed into the abnormally large volume of blood which traverses the pulmonary circulation. Upon its arrival in the left side of the heart a portion of it takes the normal circulatory path across the aortic valve and to the periphery (204). The remainder is shunted back to the right side of the heart and through the pulmonary circulation; upon its return to the left side, a fraction is again shunted from left to right. Consequently, the dilution curve obtained from a systemic artery has a low peak concentration and an abnormally prolonged descending limb. Injections into the right side of the heart are therefore of value in detecting left-to-right shunts when these exceed approximately 25 per cent of the pulmonary blood flow (30, 198). The site of injection in the right heart has little influence on the general configuration of the curve, and such curves are of no value in the localization of left-to-right shunts.

In contrast, it has been observed in this clinic (5, 27, 28, 84), and elsewhere (38, 181), that the injections of indicator into the left side of the heart and aorta are of considerable value in localizing left-to-right shunts. When the injection is made distal to the origin of a left-to-right shunt, all of the dye follows the normal circulatory path across the aortic valve and into the peripheral circulation. The resultant

dilution curve has a steep ascent and slightly slower descent but returns to the base line before the appearance of recirculating indicator. When the injection is made proximal to the origin of a left-to-right shunt, however, only a portion of the indicator takes the normal circulatory path; the remainder is shunted across the defect and through the pulmonary circulation. The late appearance of this fraction of the indicator in the peripheral artery abruptly interrupts the descending

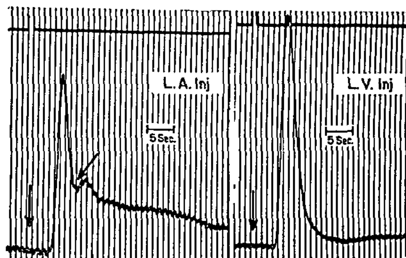


FIG. 4.—Indicator-dilution curves recorded from a peripheral artery after injection of indigo carmine into left atrium (*L.A.*) and left ventricle (*L.V.*) of patient with uncomplicated atrial septal defect (23). Vertical arrows, time of injection. Oblique arrow on curve after left atrial injection, appearance of indicator which has passed across defect.

limb of the normal curve and results either in a secondary peak or in an abrupt change in the slope of the descending limb.

Thus, in a patient with an atrial septal defect, injection into the left atrium produces an abnormal curve while injection into the left ventricle results in a normal curve (Fig. 4). We have found this application of the indicator-dilution technic to be particularly useful in the preoperative study of patients with this and allied anomalies. An abnormal curve after left ventricular injection in such patients always indicates the presence of a complicating lesion, such as mitral regurgitation or an associated ventricular septal defect. Indicator-dilution curves have also been of considerable value in determining the drainage path of pulmonary veins entered during the course of right heart catheterization. The injection of dye into such a vein yields a curve

with an early appearance time and a contour which resembles that following left atrial injection if the vein drains normally into the left atrium. Conversely, in the presence of anomalous pulmonary venous drainage into the right atrium, the appearance time is prolonged and the contour resembles that following right atrial injection (20, 179). The recent development of a tricarbocyanine dye (cardio-green) by Fox and associates (68, 70) has made possible the recording of dilution curves in whole blood independent of variations in blood oxygen

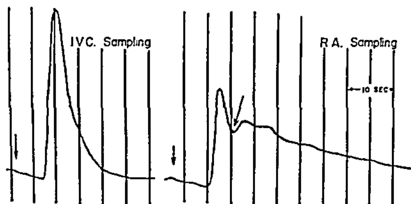


FIG. 5.—Indicator-dilution curves recorded after femoral vein injection with sampling of inferior vena cava *(I.V.C.)* and right atrium *(R.A.)* of a patient later proved at operation to have an atrial septal defect. Oblique arrow in right atrial curve, indicates presence of dye which has recirculated through defect.

saturation. The dye permits the recording of satisfactory arterial dilution curves in patients with right-to-left shunts of changing magnitude, since its maximal light absorption occurs at that wave length at which the light transmission of both reduced and oxygenated hemoglobin are identical (800 μ). This is not possible with blue dyes, since their light absorption properties resemble those of reduced hemoglobin. Tricarbocyanine dye has also extended the use of indicator-dilution curves in patients with left-to-right shunts. After indicator is injected into the pulmonary artery or left atrium (131), a dilution curve may be recorded by sampling in the right heart upstream (proximal) to the injection site. The early appearance of dye in the right heart blood establishes the presence of a left-to-right shunt. The left-to-right shunt may be localized by varying the sampling site, since no early appearing indicator will be detected in the chamber proximal to the site of entry of the shunt. Similar studies have also been carried out with I^{131}-labeled albumin (50). When arterial and right heart dilution curves

are recorded simultaneously, the magnitude of the left-to-right shunt may be estimated (204a). This method, which can detect even small left-to-right shunts, requires the insertion either of 2 catheters or of a double-lumen catheter, a maneuver which may be difficult, particularly in children.

Recently, we have recorded indicator-dilution curves from the right side of the heart and pulmonary artery following peripheral venous injections of cardio-green (29). When the site of sampling is distal (downstream) to the entry of the left-to-right shunt, the descending limb is interrupted by the presence of dye which has been shunted from left to right. When the site of sampling is proximal to the entry of the left-to-right shunt, the primary dilution curve is followed only by that portion of the indicator which has recirculated normally (Fig. 5).

In addition to Evan's blue (30, 182), indigo carmine (24), methylene blue (69), tricarbocyanine (68, 70), and I^{131}-labeled albumin (50), hypertonic saline in conjunction with a conductivity cell (16) and solutions of cold saline with a thermistor (144) have been used as indicators in the recording of dilution curves in patients with congenital heart disease. The latter two substances permit an unlimited number of injections in the course of one procedure, involve nontoxic substances, and do not produce discoloration of the skin or of the blood. The recording of a curve of radioactivity concentration by means of a scintillating detector placed over the precordium after the intravenous injection of I^{131} has been found to be a simple, reliable technic for the detection of left-to-right shunt without the need for cardiac catheterization (47a).

ANGIOCARDIOGRAPHY

Venous Angiocardiography

In our opinion, angiocardiography remains the most definitive diagnostic technic for the study of patients with the cyanotic forms of congenital heart disease. Venous angiography readily permits confirmation of the diagnosis of tricuspid atresia, demonstrating a right-to-left shunt at the atrial level, early opacification of the left ventricle, and late opacification of a diminutive right ventricle (3, 33). In the presence of a single ventricle, the angiocardiogram usually shows immediate, simultaneous and total filling of the entire ventricular area (98). It is important to establish the absence of this malformation before undertaking surgical correction of a suspected large ventricular septal defect. The lateral angiocardiogram is of particular importance in the dif-

ferentiation between tetralogy of Fallot and pulmonic stenosis with patent foramen ovale. In the latter malformation, early left atrial opacification is noted, and the aorta arises in a normal fashion from the posterior (left) ventricle (46). In a similar fashion, the intravenous angiocardiogram is basic to the recognition of transposition of the great vessels (80, 117) and in the important differentiation of this anomaly from the tetralogy of Fallot. Peripheral stenoses of the pulmonary arteries may be demonstrated readily (2, 130, 149, 188). Delayed emptying of the left atrium is often observed in congenital mitral stenosis (65). Most investigators have not found venous angiocardiography satisfactory for localizing the site of outflow obstruction in either the right (79, 114) or the left ventricles (133, 136).

Peripheral venous angiography is generally of little value in the study of patients with left-to-right cardiac shunts, primarily because of the dilution of the contrast substance by the shunt. However, when the injection is made into a vein in the lower extremity of children with uncomplicated atrial septal defect, a right-to-left shunt may be demonstrated (108). Lind *et al.* (110) have studied the time course of the flow of radiopaque material through the great vessels and cardiac chambers by determining and charting the degree of opacification in biplane angiocardiograms. They found the method particularly suitable in characterizing right-to-left and left-to-right shunts. The additional information to be derived from the application of very frequent exposures (6 to 10 per second) made simultaneously in two planes has also been stressed (195).

Selective Angiocardiography

The injection of the radiopaque medium directly into a chamber of the heart or great vessel (selective angiocardiography) has added considerably to the range of usefulness of these examinations (98). There are several advantages of intracardiac over peripheral injection (93): *(1)* The procedure may conveniently be combined with, and generally follows, preliminary right heart catheterization. *(2)* The dilution of the medium during its passage through the venous bed and right atrium is avoided; this is of particular importance in patients with cardiomegaly, left-to-right shunts, or circulatory stasis. *(3)* The medium reaches the heart in a single bolus rather than in a stream and therefore more distinct sequential opacification of the cardiac chambers may be achieved. *(4)* The presence of contrast material in the right atrium, which frequently overlies and obscures the structure under particular study, is avoided.

The rapid delivery of contrast material through a cardiac catheter in the course of selective angiography and retrograde thoracic aortography requires the use of a power injecting device (75, 93). Elder and associates (59), however, have described a special catheter with a balloon which can be filled with radiopaque medium. The latter may be liberated instantaneously within the heart by a simple wire release. The contrast medium may be injected into the left ventricle by direct percutaneous puncture (11, 51, 101), by retrograde arterial catheterization, or by manipulating the catheter into the left ventricle via an atrial septal defect and the mitral valve.

Selective angiocardiography furnishes the most precise information about the site and character of obstruction to outflow from the right ventricle (92, 94, 95). Clear visualization of this region is particularly important in the preoperative study of patients with the various forms of pulmonary stenosis. Important factors in selecting patients with tetralogy of Fallot for complete repair under direct vision are the capaciousness of the outflow tract, the locus and degree of subvalvular obstruction, the size of the pulmonary artery, and the relation between the origin of the aorta and the right ventricle (93). In addition, selective angiocardiography with left ventricular injection has been helpful in the localization of the obstruction to left ventricular outflow in patients with the various forms of aortic stenosis (29c, 138a, 138b).

Selective angiocardiography is also distinctly superior to intravenous angiocardiography in the study of patients with left-to-right shunts. In our clinic, the technic of selective left ventriculography has been found particularly important in the preoperative study of patients with varieties of common atrioventricular canal (29a, 47, 93, 132). The presence and relative magnitude of mitral regurgitation, of an associated ventricular septal defect or of a left ventriculo-right atrial shunt may be evaluated (29b) (Plate 2).

In the study of patients with total anomalous drainage of the pulmonary veins into the left superior vena cava, injection of contrast medium into the superior vena cava will not usually fill the veins. However, this diagnosis can generally be made by injection into the pulmonary artery. The site of drainage of individual pulmonary veins may be determined by direct injection of the contrast substance into the vein itself (99). Selective angiocardiography is also the most sensitive technic for the demonstration of peripheral stenoses of the pulmonary artery (2). In patients with atrial septal defect, left atrial injections have been found helpful in visualizing the defect, the mitral valve, and the left ventricle (12, 99). Injections into the right ven-

tricle will visualize ventricular septal defects only in the presence of associated pulmonary hypertension (99) or right ventricular outflow tract obstruction. Lind, Wegelius, and associates (15, 109) have found that selective biplane angiocardiography with extremely rapid exposures (6 to 12 per second) and rapid injection may be quite useful in the detection of left-to-right shunts by: *(1)* temporarily reversing the shunt; *(2)* demonstrating an area of dilution of the contrast substance at the site of entry of the left-to-right shunt; and *(3)* demonstrating delayed reopacification of the right side of the heart. Selective angiocardiography with pulmonary artery injection has also been found helpful in demonstrating reflux into the right ventricle in patients with congenital absence of the pulmonic valve (45a).

Thoracic Aortography

Castellanos and Pereiras (43), in 1939, were the first to describe the retrograde injection of contrast medium into the left brachial arteries of infants in an attempt to visualize the thoracic aorta. This method has been applied extensively by Keith (97, 98) and Abrams (1). The latter uses the procedure in children below the age of 4 years and utilizes only local anesthesia. He has found this approach particularly suited in the diagnosis or exclusion of patent ductus arteriosus as well as in the evaluation of coarctation of the aorta. In older children and adults, thoracic aortography is usually carried out by retrograde arterial catheterization, generally through a branch of the right brachial artery (32, 93, 152). In addition to the detailed demonstration of coarctation of the aorta (169), this technic has found its greatest usefulness in the study of patients with left-to-right shunts originating from the aorta, generally presenting with continuous murmurs at the base of the heart (93). The diagnosis of aortic septal defect (73), ruptured (138) and unruptured (64) aneurysms of the sinuses of Valsalva, coronary arteriovenous fistulas, and ventricular septal defect with aortic regurgitation cannot be established definitively by any other technic (Plate 3).

Cineangiocardiography

The use of motion picture film for photographing the fluoroscopic image following the injection of contrast material dates back to the studies of Stewart and associates in 1941 (177). Cineangiocardiography provides a continuous record of the movement of the dye throughout the entire cardiac cycle. In complicated anomalies in which all the

chambers opacify rapidly, the sequence of filling may be determined with considerably more precision by this technic than with standard angiocardiography (83, 173). Viewing the films in motion makes opacification more obvious than studying separate exposures; ultrarapid injections are therefore not required. Multiple small injections of contrast medium may be made and films taken in different planes (193). More recently, the fluoroscopic image has been amplified many times with an image intensifier and this has been photographed either directly (193) or first displayed on a television screen and then photographed (173). Sones (173) has used the latter technic quite effectively and recently reported only one death in 623 studies.

At the present time, the chief disadvantages of cineangiocardiography are that the films cannot be processed locally and the detail which can be achieved is considerably less than that obtained by the best standard angiographic technics (83). The latter objection may be obviated to some extent by the use of 70 mm. film (194). Campeti (40) and Gramiak *et al.* (83) have found cineangiocardiography of value in the study of patients with valvular pulmonary stenosis in whom the enlargement of the right ventricular outflow tract may be observed during diastole. In patent ductus arteriosus, diastolic blanching and reopacification of the pulmonary artery has been noted (41, 83).

PHONOCARDIOGRAPHY

The graphic registration of cardiovascular sounds has served not only to increase greatly the diagnostic precision of cardiac auscultation but has also become an important diagnostic method in its own right. In many patients with relatively uncomplicated congenital anomalies the clinical impression may be confirmed by phonocardiography, and the severity of the lesion may sometimes be assessed by this technic, obviating the need for more dangerous diagnostic methods. In more complex lesions, phonocardiographic study before cardiac catheterization or angiocardiography may modify the manner in which these procedures are carried out so that more useful information is derived. McKusick's (119) recently published comprehensive treatise on cardiovascular sound has brought together the many diverse observations in this field.

The demonstration of relatively constant, wide splitting of the second heart sound in the pulmonary region has become one of the most important signs in the clinical diagnosis of atrial septal defect (101a, 119, 178). In patients with atrial septal defect and pulmonary hypertension, in whom the magnitude of the left-to-right shunt is reduced,

the interval between the two components of the second pulmonary sound is not abnormally widened (205). However, narrowing of the split is also observed when patients with uncomplicated atrial septal defect assume the erect position, presumably due to a similar mechanism (178). Another important phonocardiographic sign of atrial septal defect is the early systolic click, recorded best along the left sternal border, probably representing a snapping of the pulmonary arterial wall early during ventricular ejection. This occurs more frequently in atrial septal defect than in any other malformation (119). When a middiastolic murmur is heard in patients with atrial septal defect, it is generally associated with a large left-to-right shunt and therefore with a very high flow rate across the tricuspid valve (6). In this connection, Nadas (141) has indicated that diastolic flow murmurs in patients with left-to-right shunts are generally audible when the pulmonary blood flow exceeds twice the systemic flow. In patients with ventricular septal defects, apical diastolic rumbles are generally associated with appreciable cardiac enlargement. Conversely, absence of a diastolic rumble usually indicates that a relatively small left-to-right shunt is present (72).

In patients with isolated pulmonary stenosis, the width of the splitting between the two components of the second sound is a useful index of the severity of the stenosis; the delay of the pulmonary component during expiration has been observed to correlate in a linear fashion with the right ventricular systolic pressure (103). Another index of the severity of the obstruction to right ventricular outflow is the presence of an ejection sound. This was recorded in all 11 patients with mild pulmonic stenosis, but in only 5 of 33 patients with severe stenosis studied by Leatham and Vogelpoel (102). Careful analysis of the phonocardiogram may also be of value in the differentiation of valvular from infundibular pulmonic stenosis. In infundibular pulmonic stenosis the systolic murmur begins immediately after the first heart sound and has an earlier peak intensity than in valvular pulmonic stenosis (124); in the latter, there may also be an appreciable delay in the onset of the murmur (123). In infundibular stenosis, the systolic murmur extends only to A_2, but in valvular stenosis, presumably because of late contraction of the infundibulum, it often extends beyond A_2 (199).

In cyanotic patients with pulmonic stenosis, the differentiation of tetralogy of Fallot and "pure" pulmonic stenosis with patent foramen ovale may sometimes be accomplished by phonocardiography. In the former patients, the presence of functional overriding of the aorta permits the flow across the pulmonary orifice to continue only up to the

time of closure of the aortic valve; the systolic murmur, therefore, generally stops before A_2 (190). In the presence of a normal aortic root, the murmur extends to and sometimes beyond A_2 because of the prolongation of right ventricular ejection produced by the pulmonary stenosis (22). The reduced pulmonary blood flow in patients with the tetralogy of Fallot greatly reduces the amplitude of the pulmonary valve closure sound. P_2 was recorded in only 3 of 18 patients with *tetralogy of Fallot studied by Vogelpoel and Schrire (190). However,* P_2 was recorded in about 85 per cent of patients with normal aortic roots (103). Patients with the tetralogy frequently have a late systolic ejection sound, originating in the aorta, while the pulmonary ejection sound in pure pulmonic stenosis occurs in early systole (119).

In the phonocardiographic study of patients with continuous murmurs, the temporal relation between the peak intensity of the murmur and the second heart sound permits differentiation of patent ductus arteriosus from left-to-right shunts originating at the root of the aorta. The peak pressure gradient in patent ductus occurs later because the transmission of the pressure pulse to the descending aorta is delayed and the peak intensity of the murmur envelops the second heart sound. However, in patients with aortic septal defect and those with ventricular septal defect combined with aortic regurgitation (148), the murmur is loudest somewhat earlier, i.e., in mid- or late systole (119). The diagnosis of total anomalous pulmonary venous drainage should be considered in cyanotic patients with continuous murmurs. This murmur presumably is generated at the site of entry of the persistent left superior vena cava into the normal superior vena cava (98).

Spectral phonocardiography provides a *time–frequency–intensity* representation of cardiovascular sound and differs basically from conventional oscillographic phonocardiography in that the frequency spectrum of the sounds is portrayed (74, 120). This technic has been applied extensively by McKusick and associates (121) to a wide variety of congenital cardiac malformations. In a spectrographic comparison of the frequency ranges of heart murmurs, Harris and co-workers (90) observed that the maximum frequency of functional murmurs was 370 cycles per second while organic murmurs extended to 800 to 1,300 cycles per second.

Intracardiac Phonocardiography

The recording of sounds and murmurs from within the heart and great vessels (intracardiac phonocardiography) now permits accurate localization of the origin of murmurs. This technic appears to be one which will both facilitate anatomic diagnosis and provide a physiologic

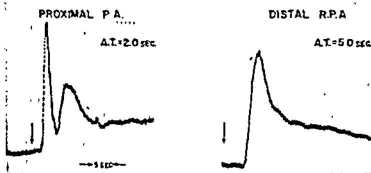


PLATE 1.—Indicator-dilution curves recorded from femoral artery after injection of tricarbocyanine dye into proximal pulmonary artery (*P.A.*) and distal right pulmonary artery (*R.P.A.*) of 6 year old girl with pulmonary hypertension and bidirectional shunts through a ventricular septal defect and through a patent ductus arteriosus. When dye was injected into main pulmonary artery, i.e., proximal to patent ductus, some dye by-passed the pulmonary circulation, resulting in an early appearance time (*A.T.*) and an early peak. When dye was injected distal to origin of the right-to-left shunts, the appearance time was longer. Prolonged descending limb results from left-to-right shunt. Vertical arrows, time of injection



PLATE 2 (left).—Lateral view selective angiocardiogram of patient with incomplete atrioventricular canal (ostium primum type of atrial septal defect with incompetent mitral valve) (93). Urokon injected into left ventricle *(LV)*, resulting in immediate opacification of left atrium *(LA)* via incompetent (left) mitral valve.

PLATE 3 (right).—Retrograde thoracic aortogram of patient with aorticopulmonary window; dye is seen in main pulmonary artery before it has passed transverse aortic arch (84)

basis for the origin of cardiovascular sounds. A variety of microphones have been employed. Lewis and associates (105, 106, 107, 191) have mounted a hollow, cylindric barium titanate element directly near the tip of a cardiac catheter. Moscovitz and associates (139, 140) have worked with a diaphragm at the tip of a catheter which impinges on a barium titanate crystal (197). Other workers have adapted inductance type transducers (101, 175), or condenser microphones (207). Luisada and Liu (115) simply employ the column of fluid within a catheter as the carrier of the sound waves; the output of the strain gauge is differentiated, filtered, and recorded on a phonocardiograph.

Murmurs are transmitted in a characteristic manner within the heart and great vessels and generally follow the path of the blood stream. Thus, in uncomplicated patent ductus arteriosus, a continuous murmur can usually be recorded only from within the pulmonary artery. In pulmonic stenosis and in atrial septal defect (116), the systolic ejection murmur is audible in the pulmonary artery; in aortic stenosis, it is heard in the aorta; while in ventricular septal defect the holosystolic murmur appears only in the right ventricle (106, 107).

In patients with the tetralogy of Fallot, without left-to-right shunts, the murmur from within the right ventricle is usually absent. The diastolic murmur in atrial septal defect has been localized to the right ventricle. This lends further support to the concept that this murmur is produced by increased flow across the tricuspid orifice. Diastolic "flow" murmurs have also been recorded from within the esophagus of patients with atrial septal defect in whom they could not be detected on the chest wall (156). The frequency characteristics of intracardiac sounds may also be elucidated by combining the technics of intracardiac and spectral phonocardiography (107). The latter approach will undoubtedly further refine our understanding and increase the diagnostic yield of clinical auscultation.

ELECTROCARDIOGRAPHY

Correlation of the ECG with the anatomic and physiologic findings in patients with congenital heart disease has greatly extended its clinical value. The chief virtue of the ECG is that it indicates the presence of chamber hypertrophy and often suggests the severity of the hemodynamic abnormality (34). In addition, serial ECGs may indicate progression in the severity of an abnormality such as pulmonary hypertension, or its regression after successful surgical treatment. Cabrera and Monroy (36, 37) have also shown that the ECG may be capable of determining whether the hemodynamic burden represents increased pressure development or increased ventricular output.

The diagnosis of ventricular hypertrophy may be established with considerable confidence if the normal limits of voltage and ventricular activation time for a particular patient are exceeded (25). The application of such criteria has been found more useful in the detection of right than of left ventricular hypertrophy, and their diagnostic accuracy has been proved in a series of cases studied postmortem (10). The value of lead V_{4R} in the detection of right ventricular hypertrophy has been stressed (39). In adults, an R/S exceeding 1.0 in V_{4R} is vir-

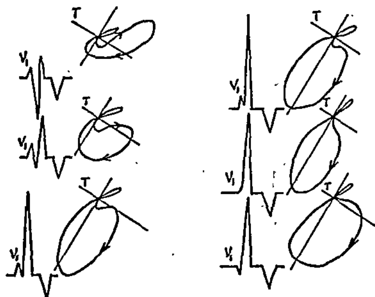


FIG. 6.—Contours of horizontal plane vectorcardiograms in patients with right ventricular hypertrophy and corresponding electrocardiographic lead V_1 (25).

FIG. 7.—Vectorcardiograms of various patients. A, Horizontal plane (H), sagittal plane (S), and frontal plane (F) vectorcardiograms of 24 year old woman with patent ductus arteriosus, pulmonary hypertension, and reversal of flow; right ventricular hypertrophy is evidenced by anterior and rightward displacement of QRS loop, with clockwise rotation in horizontal plane (26). B, 21 year old woman with ostium primum type of atrial septal defect; in frontal plane, loop is directed superiorly and to the left (56). C, 4 year old boy with interventricular septal defect; balance of electric forces is normal, and terminal appendage is oriented to right and superiorly and inscribed at normal speed; latter is a normal variant and was responsible for RSR′ configuration in patient's ECG (26). D, 6 year old boy with interventricular septal defect; terminal appendage is inscribed to right, superiorly, and anteriorly, resulting in electrocardiographic configuration of complete right bundle-branch block (26). E, 18 year old boy with coarctation of aorta; vectorcardiogram reveals left ventricular hypertrophy, evidenced by displacement of QRS loop to left and posteriorly; T forces are discordant to QRS forces (26).

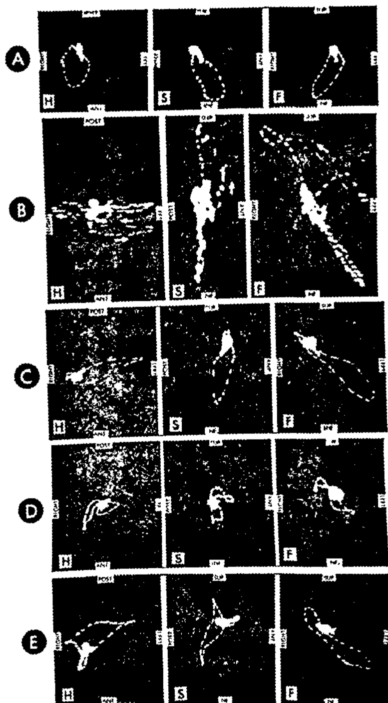


Fig. 7

tually diagnostic of right ventricular hypertrophy; this lead may be diagnostic even when lead V_1 is not. Macruz, Perloff, and Case (122) have recently presented useful criteria for the recognition of atrial enlargement. They determined the ratio of the duration of the P wave to the duration of the P–R segment and found that it exceeded 1.6 in the presence of left atrial enlargement, but was always less than 1.0 in patients with right atrial enlargement. Sodi-Pallares and associates (171) have pointed out the diagnostic value of determining the mean manifest electric axis of the ventricular activation process in patients with congenital heart disease. They have provided useful tables of the frequency distribution of the various congenital cardiac anomalies in each sextant of the frontal plane.

The ECG is an important tool in the recognition of atrial septal defect. An RSR′ configuration in lead V_1 has been observed in 40 per cent (26) to 90 per cent (6) of patients with this anomaly. While this electrocardiographic pattern has been termed "right bundle-branch block," the vectorcardiogram in most such patients has not shown a conduction defect (27, 56), and the onset of right ventricular contraction is usually not delayed (18, 27). The RSR′ pattern is thought merely to indicate the particular configuration followed by the early portion of the vector loop in the horizontal plane (26) (Fig. 6).

The ECG and vectorcardiogram are particularly important in the recognition of malformations of the atrioventricular canal (128, 184), and therefore in the distinction of the ostium primum and the septum secundum types of atrial septal defect (13). The typical electrocardiographic configuration in the presence of any of the forms of common atrioventricular canal (184) has been found to consist of: *(1)* an RSR′ pattern in right precordial leads; *(2)* left axis deviation; *(3)* a QRS loop, as projected on to the frontal plane, which rotates counterclockwise, and is generally superior to the isoelectric point. In some instances, a flattened, horizontally disposed figure-of-eight configuration of the QRS loop may be noted (Fig. 7); and *(4)* a P–R interval which may be prolonged. This basic pattern may be modified by the presence of pulmonary hypertension or by gross left ventricular enlargement due to mitral regurgitation.

Left axis deviation is an important diagnostic finding in patients with cyanotic congenital heart disease. While its presence supports the diagnosis of tricuspid atresia (33, 142), or of single ventricle (142), it has also been noted occasionally in a variety of other malformations (26). In a series of cases proved at autopsy studied by Neill and Brink (142), electrocardiographic signs of left ventricular hypertrophy were found in 27 of 28 patients with tricuspid atresia but in only 3 of 8

patients with single ventricle. The high, peaked P waves in patients with tricuspid atresia were generally associated with small interatrial communications. An ECG showing left ventricular hypertrophy is also a characteristic finding in primary endocardial fibroelastosis (189). The absence of electrocardiographic evidence of myocardial necrosis is useful in the differentiation of this lesion from anomalous origin of the left coronary artery. Tall, peaked P waves and an RSR′ configuration in right precordial leads with marked QRS prolongation is characteristic of the ECG in Ebstein's anomaly (99, 186).

Vectorcardiography

Spatial vectorcardiography appears to be more sensitive than scalar electrocardiography in the detection of both right and left ventricular hypertrophy (26, 56). By means of the vectorcardiogram, patients with an RSR′ configuration in right precordial leads can be separated into the following 4 groups (25–27, 56): *(1)* right ventricular hypertrophy without conduction defect; *(2)* right ventricular conduction defect without right ventricular hypertrophy; *(3)* combined right ventricular hypertrophy and conduction defect; and *(4)* no conduction disturbance or ventricular hypertrophy (Fig. 7; Plate 3). Silverblatt and associates (167) have recorded vectorcardiograms showing right ventricular hypertrophy in 29 of 30 patients with atrial septal defect. In such patients, the QRS loop in the horizontal plane is generally narrower than in patients with pulmonary stenosis or pulmonary hypertension (87). The validity of the vectorcardiographic criteria of right ventricular hypertrophy has been proved in a group of cases which subsequently came to postmortem examination (10).

Intracardiac Electrocardiography

The intracardiac ECG also appears to be a helpful diagnostic tool in a number of congenital malformations. Several groups of investigators have observed that in Ebstein's anomaly a right ventricular intracardiac potential can be recorded from an area which lies to the left of the spine, but from which a right atrial pressure pulse is recorded. As the catheter is withdrawn, an abrupt transition to a right atrial cavitary potential occurs without change in the contour of the pressure pulse (91, 172, 208). In patients with a single ventricle, no R wave is present in the intraventricular ECG, since septal depolarization does not occur (61). The intracardiac ECG has also been found of value in the localization of the site of obstruction in the right ventricular outflow tract. As the catheter is withdrawn from the pulmonary artery to

the right ventricle in patients with valvular stenosis, an abrupt change occurs simultaneously in both the pressure pulse and the intracavitary ECG. On the other hand, in infundibular stenosis, the intracardiac ECG changes before the pressure pulse (62).

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Indications for and Results of Surgical Treatment of Congenital Heart Disease

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WITH THE GREAT ADVANCES in surgical treatment, this subject now covers a very wide field. In some directions the advances are too recent for any definitive views but will be referred to briefly.

Six forms of acyanotic congenital heart disease—persistent ductus arteriosus, atrial septal defect, ventricular septal defect, pulmonary stenosis, aortic stenosis, and coarctation of the aorta—are about equally common, except that the last two together make up only about one-fifth of all acyanotic cases. With cyanotic forms, on the other hand, Fallot's tetralogy accounts for two-thirds of them.

PERSISTENT DUCTUS ARTERIOSUS

INDICATIONS FOR OPERATION.—Since such treatment became possible, many physicians have thought that all patients should be operated on because of the relatively early ages of death of most reported cases. Children are often so well and leading such active lives that their parents are reluctant to accept any great operative risk. At first, therefore, I advised operation only for those with a large shunt and a large heart, but in a follow-up of all the patients over 35 whom I could find most were becoming more disabled. I then came to the conclusion that a persistent ductus should always be closed, unless there were signs that it was very small or that it was already closing spontaneously (8). It is not worth waiting for the chance of this happening since it occurs too

rarely, although in 1 of my child patients who came in for operation recently the ductus had closed.

This general rule must not be applied to patients who have some other malformation as well as a ductus, for then it may be the main blood supply to the lungs, nor to those who have right ventricular preponderance or any hint of cyanosis; such patients should be fully investigated by catheterization. Right ventricular hypertrophy may be due to the presence of other malformations or to pulmonary hypertension. The latter is a further indication for operation, provided the shunt is still mainly left to right, for then pulmonary hypertension is generally completely reversible; but if the shunt is mainly right to left, it is not.

The decision may be more difficult in older patients, but operation can be successful even in those over the age of 50. A 53 year old woman had severe attacks of left ventricular failure, but 3 years after operation she is leading an active life without symptoms. If, however, there are no symptoms and the heart is of normal size after the age of 35, the patient will probably remain well without operation.

Operative mortality.—This has now become low, and several workers have reported series with only a few deaths. There was only 1 death in 119 uncomplicated cases of my own, and this included 8 patients over 35 years of age and several with pulmonary hypertension. There were, however, 4 deaths in more complicated cases; in 2 the shunt had become reversed or balanced and in the other 2 there was recanalization after operations performed elsewhere.

A low mortality is essential for patients who are as well as most of these are, and for this reason I favored ligation of the ductus rather than its division. I have rarely seen recanalization of the ductus, but scattered reports from other clinics show that it happens with some frequency. It is now much easier to advise operation as a routine, and to approve division of the ductus, for there is general agreement that in the hands of competent thoracic surgeons the mortality should not exceed 1 per cent.

Results.—Apart from the risk of recanalization after ligation of the ductus, few late complications have been reported (29a). I do not know any large series of patients who have been followed for a long time, perhaps because so many patients that have been followed for a year or two after operation have all been so well that a lasting good result has been assumed.

In younger patients, a large heart often reverts to normal size, but a dilated pulmonary artery does so more slowly, and completely only if its large size can be compensated for by the patient's growth. In those

who are older, the heart becomes smaller but there is less chance of it reaching normal size.

Normal rhythm cannot always be restored if there has been auricular fibrillation for some time. Thus, in 3 patients between 30 and 40 years old, operated on since my series was reported (8), 1 with fibrillation of recent onset reverted to normal rhythm and her heart became almost normal in size, but in the other 2, both with large hearts and a longer period of fibrillation, normal rhythm could not be restored even with quinidine, though the hearts became smaller.

ATRIAL SEPTAL DEFECT

INDICATIONS FOR OPERATION.—The outlook is worse than for a persistent ductus, for many patients become disabled in the fourth or even in the third decade. In some, congestive failure develops from the strain of the large flow; in others, pulmonary hypertension develops and then the shunt may become reversed or there may be pulmonary thrombosis (15).

For some years it has been thought that most atrial septal defects should be repaired as soon as operation became satisfactory. This time has now arrived, and all patients should have the defect closed except if it is very small, or the pulmonary changes have progressed too far, or other associated malformations are a contraindication. This applies to ostium secundum defects. Ostium primum defects may be suspected when severe symptoms develop early or when there is evidence of left ventricular involvement. The sinus venosum defect often associated with anomalous pulmonary veins draining into the right atrium can be dealt with in the same way as ostium secundum defects, but ostium primum defects generally require an assisted circulation.

TYPES OF OPERATION.—Surgical relief of ostium secundum defects has been carried out in several ways. Blind operations have been performed by suturing the right atrial wall to the margins of the defect, and this has been improved by the "atrial well" method (27). Søndergaard (36) introduced an ingenious method of circumclusion by suturing the defect along the lines of the septum. Successful results have been reported from several centers, but none of these methods allows closure of the defect under direct vision.

With a defect that varies so much in size and position, open heart surgery has always seemed desirable. With hypothermia, this method has now been developed by Swan *et al.* (38, 39), by Blount *et al.* (2), by Brock and Ross (5), and by Bedford *et al.* (1), and seems likely to become the standard procedure.

Operative mortality.—When only patients in the late stage of the condition who could not afford to wait were operated on, the mortality was high. If the pulmonary arteriolar resistance has risen, so that the left-to-right shunt has become small and there is a right-to-left shunt, successful operation is rarely possible.

At present, it is hard to give reliable figures, for the conditions vary so widely. For open operations under hypothermia, Bedford *et al.* (1) have reported a series of 40 patients operated on by Mr. Holmes Sellors, with 1 death. More recently, Chin and Ross (16) have reported on 49 cases with 4 deaths among the first 10 and none in the subsequent 39. Perhaps one can say that the operative mortality has fallen from 10 to about 5 per cent, but the aim must be to reduce it to as low a level as for persistent ductus.

Results.—Good results have been reported by the closed methods (36). Edwards *et al.* (23) found that 9 of 11 patients were doing well and in 4 the hearts had become much smaller. Gøtsche and Søndergaard (25) have reported the results in 27 patients treated by their "circumclusion" method: catheterization suggested the defect was closed in 17 and the shunt was much smaller in the other 9 patients.

In the series of Bedford *et al.* (1), 12 patients had been recatheterized: in 7 the findings were completely normal and in 3 others there might still have been a small shunt, though the increase in arterial oxygen saturation was not enough to prove this. In 2, however, appreciable shunts persisted; even 1 of these showed a very good result, for a large heart had become smaller, and she had lost her heart failure and been able to return to work.

No large series has been followed for long and one will have to wait to learn how regularly the defect can be completely closed and how constantly the heart can be restored to normal size. The factors that have been discussed for a persistent ductus, such as age and the duration of pulmonary hypertension and of auricular fibrillation, will probably be found to apply here also.

VENTRICULAR SEPTAL DEFECT

Indications for operation.—The need for surgical treatment in this condition is greater because the prognosis without it is much worse. Except for the relatively few cases with the classic picture of Roger's disease, in which the shunt is no more than 3 liters a minute through a small defect, all isolated ventricular septal defects without irreversible changes in the lungs should be closed as soon as this can be done with reasonable safety.

If the heart is enlarged, if the lung fields are engorged, if there is right or left ventricular hypertrophy or both in the ECG, or if there are cardiac symptoms, the defect is large enough to need closing because of the poor prognosis. The pulmonary pressure is probably near the systemic level, and the arteriolar resistance is likely to rise and the shunt to become reversed (6); the changes in the lungs will then prevent a successful operation. We do not know yet what level of pulmonary arteriolar resistance makes success unlikely. The patient should benefit when it is 6 units* or less (normal, 1 to 3 units) but not when it is near 20 units. This leaves many cases in between where more experience is needed, though DuShane *et al.* (22) seem to have obtained some good results with resistances between 7 and 17 units. The continued presence of a large left-to-right shunt may prove the most useful measure, although at present not if there is associated aortic regurgitation.

Operative mortality and results.—There is no large series of patients who have been recatheterized or followed for any length of time. However, in many patients successful closure of the defect is evidenced not only by the clinical improvement, but also by the decrease in heart size, by the much lower pressure in the right ventricle at the end of the operation, and by the findings with indicator-dilution curves.

There is general agreement that these operations can only be performed with an assisted circulation, and many forms of this have been tried during the last few years. Largely because of these difficulties, the operative mortality has been about 30 per cent. Although this is becoming much better at several centers, it is not easy to learn the total mortality from some of the reports. DuShane *et al.* (22) reported 4 deaths among their last 20 patients, and Brock (4a) has had 2 deaths in the last 12 cases. Cleland *et al.* (18) have had 4 deaths in the last 21 cases, but only 1 in the last 15 uncomplicated cases.

All of them, as well as Warden *et al.* (41) and Gerbode *et al.* (24) have reported good results; Kirklin *et al.* (33) thought with some supporting evidence that in 18 of their last 25 patients the defect had been successfully closed with great benefit. Probably it will not be long now before the difficulties presented by the assisted circulation will be overcome, but at present the operation should be done only at centers with special facilities. The closure of the defect appears to be

* Unit of vascular resistance is defined as V,

$$\frac{\text{mean arterial} - \text{mean venous pressure (mm. Hg)}}{\text{mean blood flow (L./min.)}}$$

less difficult than might have been expected, and there seems good reason to hope that the operation will become a standard and successful one.

COARCTATION OF AORTA

Indications for operation.—All patients with coarctation should, we think, have surgical treatment unless the narrowing is too slight to produce much rise in the systemic blood pressure. This certainly is true for all patients under 20 years of age. We were led to this view particularly by finding that 6 patients who were in reasonably good health when they were first seen had died within 2 or 3 years (11), and since then 2 more young patients have died, making 8 in all: a girl of

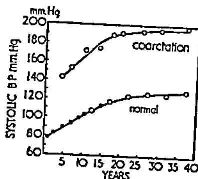


Fig. 1.—Rise of systolic pressure with age in coarctation of the aorta, compared with that in normal subjects. Rise is more rapid in patients with coarctation up to about the age of 17.

9 with congestive heart failure after she had been cured of bacterial endocarditis; a boy of 8, whose blood pressure 3 years earlier had been only 130/80, and a man of 27, both from cerebral hemorrhage; a man and a woman, both aged 22, suddenly from a ruptured aorta; the other 3, all with aortic regurgitation, of congestive heart failure at the ages of 17, 27, and 28. The third decade seems to be a period of particular danger.

One cannot say exactly how many patients were at risk and for how many years, though a few had been under observation for as long as 25 years. There are about 660 patient-years to cover the 8 deaths, a little more than a death a year for each 100 patients. This implies that an operative mortality of 5 per cent would be covered in the first 5 years after operation.

Significance of aortic regurgitation.—If this is present and not too severe, it is a further indication for surgical treatment, for regurgitation is likely to become progressively worse; this may be arrested if the blood pressure is reduced by a successful operation. If, on the other

hand, it has progressed to the stage where the diastolic pressure has fallen to 70 or 80 mm. Hg. relief of the coarctation is not likely to help.

OPERATIVE MORTALITY.—In our first 60 patients the mortality was 12 per cent, but this included some with congestive heart failure; only 1 of the last 20 patients has died. In a recent analysis of 648 reported resections, there were 45 deaths, an incidence of 7 per cent (11), but this, of course, included early operations by many surgeons. We think

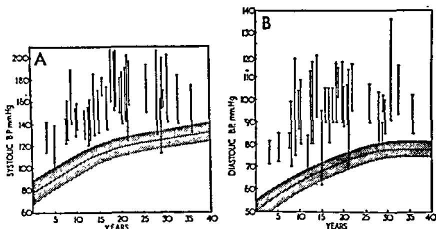


FIG. 2.—Improvement in systolic (A) and diastolic (B) pressures of patients with coarctation of the aorta after operation. Shaded area, the normal curve shown in Figure 1, with a range of about 10 per cent above and below this; as may be seen, in all the patients the pressure is nearer the normal, but is still somewhat above it in most.

the mortality for competent thoracic surgeons is now under 5 per cent and Gross (26) reports only 2 deaths in his last 100 cases.

RESULTS.—Most studies of patients after resection have reported the blood pressure as normal or reduced without much detail; Hallenbeck *et al.* (28) report it as below 130/90 in 49 per cent, Gross (26) as below 140, with corresponding reductions for children, in 88 per cent, and Walker and Haxton (40) as an average fall of 47/24 mm. in 25 cases. More detailed studies by Counihan (19) and Cleland *et al.* (17) find that although the brachial blood pressure is much reduced it rarely falls to normal. The average pressure in their cases before operation was 177/99 and after it 157/87 mm.

The results in our first 30 patients surviving with a completed resection have been reported earlier (11). We believe that the length of follow-up is more important than the size of the total series, and our

discussion will therefore be limited to these cases, which have now been followed for nearly 6 years. All of the patients improved, as judged by a fall of blood pressure and by a loss of symptoms if they had any. The fall in blood pressure must be gauged by what is normal for the patient's age (Fig. 1). The average pressure fell from 180/106 to 135/83, a fall of 40 mm. in the systolic and of 20 mm. in the diastolic pressures. It did not generally fall to normal (Fig. 2), and there were 12 patients with diastolic pressures of about 90 but only 1 in whom it was over 100 (102, but the systolic pressure had fallen from 207 to 157).

The figures for each patient were the average of all readings re-

TABLE 1.—FALL OF BLOOD PRESSURE IN 30 PATIENTS AFTER OPERATION FOR COARCTATION OF THE AORTA

Group	Preoperative Blood Pressure		Postoperative Blood Pressure: After 3½ yr.		Postoperative Blood Pressure: After 6 (3-10) yr.	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
10 patients with highest diastolic pressure	193.5	118.5	142.8	90.2	150.5	92.6
10 patients with second highest pressure	180.6	107.3	138.6	84.1	136.4	81.5
10 patients with lowest pressure	164.9	92.7	124.3	75.6	126.9	78.9
Average of all	179.9	106.2	135.2	83.3	137.9	84.3

corded by various observers. Before operation, they represent a large number of readings and are, we think, near the true level; after operation, they represent several readings but not so many. It is, of course, easy to record the lower readings and neglect the higher ones, but we took them under the same conditions and they are about 10 mm. higher than the average figures obtained in the ward after operation.

The results (Table 1) show that the improvement after 3 years is unchanged after 6 years, for half the slight increase in the systolic pressure and nearly all the still smaller increase in the diastolic pressure (1 mm.) was accounted for by one 33 year old man whose pressures had risen to their previous levels, though he is still free from the severe headaches that had interfered with his work before.

AORTIC REGURGITATION.—The position with regard to this may be illustrated by 3 cases. A 6 year old girl had a faint aortic diastolic murmur that was heard on most but not all occasions; after operation the blood pressure was 127/82 instead of 158/112 and no diastolic murmur was heard during the subsequent 3 years. A man of 36 had moderate

regurgitation; 5 years after operation he is better, with a blood pressure that has fallen from 174/101 to 140/80, though he still has some symptoms and the regurgitation seems the same. A man of 29 had more severe regurgitation and the blood pressure was 213/77. His operation was successful in the sense that the blood pressure fell to 163/57, but his symptoms were hardly relieved and a year later he died with left ventricular failure.

These cases show that if aortic regurgitation is slight it may disappear after operation or, at least, fail to become established; that if it is moderate, it may not prevent a good result for several years; but that if it is severe, there may be little improvement from operation and the patient may die from the effects of the aortic regurgitation.

CARDIAC SIZE AFTER OPERATION.—The heart is often of normal size and rarely very large except with free aortic regurgitation. In 20 of our patients there was no general enlargement, although some hypertrophy of the left ventricle was doubtless present. In the other 10, whose hearts were enlarged, it has become a little smaller since operation, but as the larger hearts are generally in adults a return to normal is less likely.

ELECTROCARDIOGRAPHIC CHANGES.—About a third of our patients have shown left ventricular strain, with T waves that were flat or slightly inverted in leads V_5 and V_6. These signs have nearly always been lessened by a successful operation, and in about half our patients they have disappeared. It is surprising how many do not reach a stage where left ventricular preponderance can be diagnosed decisively on the ECG alone. When present, it has become less after operation but less constantly than the improvement in signs of left ventricular strain.

DISCUSSION

There has been a tendency to assume that when the pressure does not fall to normal, the surgeon has not relieved the obstruction completely, but Counihan (19) doubts this and found no precise relation between the fall of blood pressure and the apparent increase in the aortic diameter at the anastomosis. Donald *et al.* (20) studied the cardiac output and the systemic pulmonary arterial pressures before and after operation. They found evidence of incipient left ventricular insufficiency in many relatively young patients who denied disability. After operation, even in very successful cases, they found that the behavior of the systemic blood pressure was still abnormal.

Except for the death of the patient with gross aortic regurgitation, there have been no complications among our patients. Nor have we

found many reports of such complications. One death from bacterial endocarditis has been reported. Aortic regurgitation has developed in one boy of 15 despite a successful resection (34).

Most follow-ups are not long and we shall not know the real outcome of operations for coarctation until several large series have been followed for 20 years, for we do not know how great the remaining risks may prove to be—the risks of subacute bacterial endocarditis on bicuspid valves, of rupture of berry aneurysms of the cerebral vessels, and of rupture of the aorta. They should be much less with the improvement in blood pressure, but the last two groups have not been closely related to the height of the blood pressure and the damage to the arterial media may already have taken place, even if it was not an independent congenital lesion. The site of the anastomosis and the graft itself, when this has been used, may not always remain satisfactory. Even if these complications do occur from time to time and if, as Donald *et al.* (20) have shown, the behavior of the blood pressure is not always as normal as it seems, the possibility of avoiding these limitations will not be settled until large series of children who have been operated on before the age of 5 have been followed for many years.

CONGENITAL AORTIC STENOSIS

INDICATIONS FOR OPERATION.—Sudden death is not uncommon in these children and the prognosis is not as good as has been thought. Yet the selection for operation is difficult, because many of them do well until 30 or 40 years of age, when the valve has become calcified. Anginal pain in children may be mild and hardly noticed, so should be enquired for carefully. This or syncopal attacks on exertion or signs of left ventricular strain in the ECG are the best indications for operation.

OPERATIVE MORTALITY.—This is still relatively high, probably 10 per cent in most series. Further, the surgeon cannot be certain whether he can avoid producing aortic regurgitation. Even if the patient feels better when the stenosis is relieved, regurgitation must inevitably be a serious drawback, with a risk of left ventricular failure.

RESULTS.—The results may sometimes be very good.

SIMPLE PULMONARY STENOSIS

This is a useful term for pulmonary valvular stenosis with a closed ventricular septum, whether the foramen ovale is unsealed, when central cyanosis can and will develop if the stenosis is severe enough, or

whether it is sealed, when there cannot be any central cyanosis however high the right ventricular pressure.

INDICATIONS FOR OPERATION.—There may be severe stenosis and a high right ventricular pressure although there are few signs or symptoms to reveal it, since the right ventricle can hypertrophy enough to maintain a normal blood flow to the lungs for years. By the time there are significant symptoms and still more by the time there is general enlargement of the heart, the condition is advanced; while operation is still possible then, the best time for this has passed.

The ECG gives an earlier indication. Right ventricular strain with T inversion from V_1 to V_4 indicates a right ventricular systolic pressure over 100 mm. Hg and the stenosis should be relieved. However, the pressure may be as high as this before these signs develop, and often catheterization is necessary before deciding whether immediate or future operation is necessary. If there is no right ventricular preponderance, the pulmonary gradient is probably slight and operation is not needed; if this is still true when the patient is 20, it is unlikely that it will ever be needed.

There has not yet been much opportunity of learning how much and how fast the gradient across the pulmonary valve is likely to rise with age. The level that demands operation has not yet been settled on good evidence. Empirically, I accepted a right ventricular pressure of 100 mm. or a gradient of 80 mm. as a firm indication for operation. Kirklin *et al.* (32) and Blount *et al.* (3) have suggested that a pressure of 75 mm. (or a gradient of 55 mm.) is enough. The gradients that do and those that do not prevent good results after operation are pertinent: gradients of 30 mm. do not prevent good results, but those of 50 may do so.

In summary, the following patients need operation: *(1)* All who are cyanotic or have cardiac symptoms. *(2)* All who have large hearts, but this is a late sign. *(3)* All who have large *a* waves in the jugular pulse or large P waves or right ventricular strain in the ECG. All who have gradients across the pulmonary valve of 50 mm., or perhaps even 40 mm. in children. Gradients of 30 mm. or even a little higher seem to be unimportant and, so far as we can judge, are likely to remain so.

OPERATIVE MORTALITY.—There were 11 deaths at or immediately after operation among our 75 patients, but 5 of these were among the first 6 operated on and several of them were gravely ill with congestive failure. Among the 6 later deaths, 2 were equally advanced cases and 2 were during the early stages of using hypothermia. In several early series the mortality was about 10 per cent, but for experienced surgeons it is now well under 5 per cent.

RESULTS.—Valvotomy for simple pulmonary stenosis is established as a good operation. Campbell and Brock (12) discussed the results in several small series and in their 58 patients. Of the 50 who survived, good results were obtained in 46 though often some degree of pulmonary stenosis still remained. When the heart was enlarged it generally became smaller, the cardiothoracic ratio falling from an average of 60 to 54 per cent. When there was electrocardiographic evidence of right ventricular strain, it generally became less and sometimes disappeared entirely. Of the 23 who were recatheterized, 2 showed no systolic pressure gradient across the pulmonary valve and in the others it had been reduced to about a third of what it had been before: in 13 to below 40 mm., and in 6 others to below 50 mm. Several have reported similar results. Combining 4 series (3, 21, 30, 37), most of the survivors were much better, with the gradient falling to about half or one-third of its previous level.

We are now reporting here the results in 75 patients, and are assessing these more critically. Previously, they were judged mainly on clinical grounds, improvement in the size of the heart and in the ECG being disregarded. But now, a good result means that the clinical impression was supported by objective changes: if the heart was large, that it had become smaller (Plates 3 and 4); and if there were signs of right ventricular strain that they had decreased (Plates 1 and 2). For some months after right ventricular section, the T wave inversion may be deeper but this is transient; a smaller R wave in V_1 and less right axis deviation in the standard leads are earlier signs of a successful reduction of the pulmonary gradient.

True infundibular stenosis was not often found with valvular stenosis when the ventricular septum was closed, though it so often is with tetralogy of Fallot. There were, however, 3 cases of pure infundibular stenosis among our 75, and some others in whom the greatly hypertrophied right ventricle produced varying degrees of infundibular obstruction, often with a large gradient. Residual gradients found at operation after successful valvotomy seemed likely to be of this type and the great improvement in such patients, clinically and on recatheterization, suggested that this muscular hypertrophy could regress. Kirklin *et al.* (32) have expressed similar views. Johnson (31) has found that in 8 of 10 such cases with complete data the obstruction regressed completely in spite of some residual valvular stenosis.

Our 64 surviving patients (21 cyanotic and 43 acyanotic) have now been followed for an average period of nearly 6 years, many for 7 to 8 years, and one for 10 years.

Cyanotic patients.—The results in these are easy to judge because all

the patients had symptoms and nearly always signs of right ventricular strain; about half had an enlarged heart. We have reasonably full data for all except one American girl who was doing well after 2 years.

Of the other 20 patients, 19 were much better clinically and only 2 showed any residual cyanosis. Including them, the average arterial oxygen saturation was increased from 78 to 94 per cent; the polycythemia disappeared, and the hemoglobin percentage fell from 120 to 88 per cent on the average.

The size of the heart in the 10 with a large heart decreased, and in 8 markedly. Half lost all the T inversion in the ECG and in most of the others it became less; half lost much of their right ventricular preponderance and another quarter lost some of it. Recatheterization in 8 revealed that the average systolic gradient across the pulmonary valve had been reduced from 138 to 27 mm. Hg. In our last 5 patients, in whom this has not yet been done, the gradient at operation was reduced from 74 before valvotomy to 26 mm. afterward.

The result in the last patient would have been good had not rather free pulmonary regurgitation developed. Only in 2 others, both children, did a lesser degree of this develop, and after 5 years it has not prevented clinical and objective improvement.

On the basis of these findings, all the 20 patients have greatly improved and in half an excellent result was obtained, but the last is not likely to maintain it because of fairly free pulmonary regurgitation.

Acyanotic patients.—In these, the degree of improvement may be less easy to assess since many seemed so well before operation, which was done because of the high right ventricular pressure. Only one-quarter had a large heart but three-quarters had right ventricular strain, perhaps because this was taken as an indication for operation. Only 1 failed to benefit from the operation.

Good results.—Of the 43 patients, 34 were able to resume active lives and often showed great improvement in objective signs. Of the girls, 5 have married, a much higher proportion than among those who have had operations for Fallot's tetralogy.

Tuberculosis developed in 1 boy in whom a good result was obtained; he died 6 years after operation, the only patient in the whole series who has died or even deteriorated during the follow-up. In 30 of the 34 patients, the clinical judgement was supported by objective changes, but the other 4 had few such signs before operation and have not been recatheterized. The right ventricular strain in 19 of the 20 with this sign diminished greatly and often disappeared, and the right ventricular preponderance also diminished. In 7 of the 8 whose hearts were large, cardiac size became much smaller; in the eighth, the heart

had never been very large. Recatheterization in 13 patients has shown a reduction in the average pulmonary gradient from 115 to 29 mm., and, if 7 others mentioned later are included, from 117 to 37 mm. In 6 recent cases in which this has not yet been done, the gradient at operation fell from 85 before valvotomy to 27 mm. after.

There were 4 others, all early patients, in whom the good clinical results were supported by some objective findings, though other findings suggested less complete relief of the stenosis. The first patient lost all signs of right ventricular strain, but the pulmonary gradient, which had been as high as 158, was still 78 mm. The second was very well and had a much smaller heart, but the T inversion was reversed only in V_5 and V_4: recatheterization failed in her case. The third now leads a normal life and the T inversion has been reversed in V_3 and V_2, but the gradient, which was 130, is still 60 mm. The fourth was able to be more active, her heart became smaller, and her pulmonary gradient fell from 88 to 21 mm. (mean pressures), but T still remained inverted to V_4.

Improvement only.—There were 8 patients who, by the standards of the present appraisal, are considered improved only. In 2 of these, recatheterization showed that their gradients had fallen from 103 to 14 mm. and from 109 to 45 mm., but they seemed unable to lead an active life after years of relative invalidism. The third was in a good clinical state, and the systolic gradient had fallen from 100 to 39 mm., but there was still T inversion to V_4. The fourth was improved clinically and objectively, but the T inversion was reversed in V_5 and V_4 only.

Pulmonary regurgitation developed in the fifth and this prevented her heart becoming smaller, though the pulmonary gradient had been reduced from 105 to 50 mm. The sixth also has pulmonary regurgitation; she feels better but her heart has become larger, so that in the long run she is unlikely to benefit. The seventh, who refuses recatheterization, seems better, but T inversion still extends to V_4. The eighth can do more and his ECG is better, but his pulmonary gradient is still 80 (instead of 175) mm.

Results in the first 4 might perhaps be called good, but they are disappointing in the last 4, in 2 because of pulmonary regurgitation, and in the other 2 because the stenosis has not been adequately relieved.

No improvement.—Only 1 of the 43 patients failed to benefit, probably because of a fault in surgical technic. His heart has become larger, the gradient has not been reduced much, and recatheterization revealed an unrecognized infundibular stenosis.

Discussion

When the patient's condition is improved rather than relieved, it may be because the pulmonary gradient has not been reduced adequately; this was certainly the case in some of our patients. There may, however, be great clinical improvement, a smaller heart, and less right ventricular strain, even with a moderate residual gradient. The age of the patient was important, possibly because the valve had become more rigid with age or because the myocardial changes had become irreversible. All those in whom a good result was not obtained, excluding the 3 in whom this could be attributed to pulmonary regurgitation, were between 20 and 33 years of age, while the oldest patients whose right ventricular strain pattern disappeared completely were between 19 and 23 years. It seems, therefore, that patients should be operated on before they are 25, or better before they are 20, lest the electrocardiographic changes, and presumably the myocardial changes, may have become irreversible.

Most of these operations were carried out by the transventricular route, but some more recent ones by a pulmonary arterial approach under hypothermia. I cannot say that the latter has given better results, because most recent operations have tended to produce a greater reduction of the pulmonary gradient than the earlier ones. This is also the experience of Hansen, Ikkos, and Crafoord (29) but they thought that the reported results by the transarterial route were generally better.

Blount *et al.* (3), reporting on 5 cases operated on by this method, found that the gradient was often reduced to insignificant levels such as 5 mm., but several had pulmonary regurgitation. They have since reported (4) on 38 patients operated on in this way, with only 2 deaths: 25 had been recatheterized and the gradient was under 20 mm. in 17 and between 20 and 40 in the other 8 cases. There were, however, 8 with some pulmonary regurgitation but it had not produced any harmful effects during the 3 years of follow-up. This operation will probably become the method of choice and if care is taken to avoid pulmonary regurgitation, it should be almost completely curative.

While this article was in press, a more critical evaluation of valvotomy as a curative operation for simple pulmonary stenosis has been completed (10a). Only 2 per cent of the patients failed to obtain any benefit. Thirty-eight per cent were greatly improved, clinically and objectively, but the average residual gradient was still just over 50 mm.; they cannot be regarded as cured and may again at some later

date get increasing symptoms. The results were, however, so good in 60 per cent, including similar proportions of acyanotic and cyanotic patients, that we think they nearly reach this high standard of cure. There is, however, some evidence that these small residual gradients become much higher with exercise. Perhaps the further reduction of this average remaining gradient of 28 mm. would be more likely to be achieved by open operation, but this must not be at the expense of producing more pulmonary regurgitation.

Consideration of these results has led us to decide on the smaller gradients that should be taken as an indication for operation. Theoretic calculations suggest that a pulmonary valve area of less than 1.0 sq. cm. may be a considerable handicap (10b), but until more measurements of the areas have been made, the gradients across the valve will remain a better guide.

TETRALOGY OF FALLOT

INDICATIONS FOR OPERATION.—Nearly all children with Fallot's tetralogy are sufficiently disabled to need operation. Older patients who can manage light work should probably wait till curative operations are safe and successful for the obstruction to the pulmonary flow cannot be severe. At the present stage, it is not easy to know which of the three operations to use: (1) subclavian-pulmonary or other anastomoses, (2) Brock's direct operations of pulmonary valvotomy or infundibular resection or both, and (3) open operation with closure of the ventricular septal defect and relief of the stenosis. It is too early to report the results of the last method, as no patients have yet been followed for long. Clearly, it should be pursued with vigor at centers with special facilities until the difficulties and the high operative mortality have been overcome, but only at such centers. In time, no doubt, it will become the standard method, as it is the only attempt at a cure. Valvotomy and infundibular resection will, of course, remain an essential part, so that the success they can achieve is important. Perhaps, at most centers these are still the best treatment, for they will improve the development of the right ventricular outflow tract and enable the patient to benefit fully from subsequent closing of the septal defect. The conclusions that follow are based mainly on our own published observations (10, 13, 14).

OPERATIVE MORTALITY.—At Guy's Hospital, 14 of the first 165 patients who had anastomotic operations died. This is an operative mortality of under 9 per cent and for average cases it should not exceed 5 per cent. For direct operations, the mortality is higher, 15 per cent at first, but since 1952, excluding second operations which are more

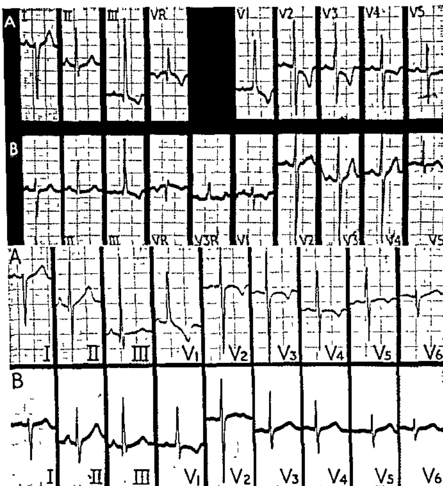


PLATE 1 (above).—Disappearance of right ventricular strain and even of preponderance after valvotomy for simple pulmonary stenosis with cyanosis. A, before operation; inversion of T wave to lead V_4. B, 3 years after operation; inversion of T wave in leads III and V_1 only, and a much smaller R wave in lead V_1, with diminished right ventricular preponderance

PLATE 2 (below).—T wave inversion before and after valvotomy for acyanotic pulmonary stenosis. A, before operation; sharply inverted T wave from leads V_1 to V_4 and slightly inverted T wave in V_6. B, 3 years after operation, T wave is less inverted in lead V_1 and is upright in all other chest leads, although notched in V_2; the Q-R ratio in V_R was 1 instead of 1:4.

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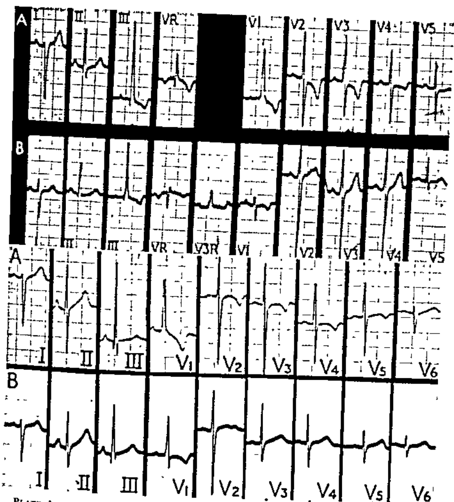


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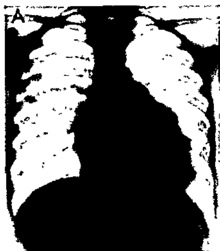
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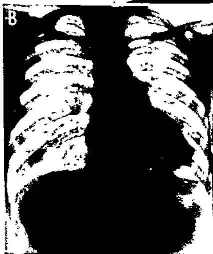
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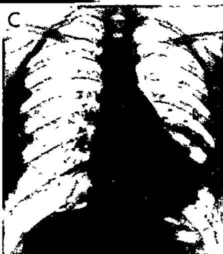


PLATE 4.—Size of heart before (A) and after (B and C) valvotomy for acyanotic pulmonary stenosis, note great reduction in size. Before operation cardiothoracic ratio was 63 per cent, 1 year after operation (B), the ratio was 54 per cent; 3 years later (C), when the patient had grown considerably and had led an active life, the increase in chest size was greater than in cardiac size, and the ratio was 53 per cent.

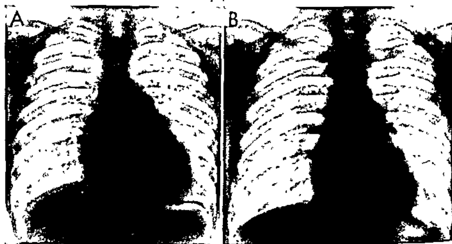


PLATE 3.—Size of heart before (A) and after (B) valvotomy for simple pulmonary stenosis with cyanosis; note great reduction in size. Before operation cardiothoracic

dangerous, under 10 per cent. Curative operations with closure of the ventricular septal defect still have a prohibitive mortality in most centers, but no doubt this will be overcome.

Results of Anastomotic Operations

Good results were obtained in 130 of our first 165 patients who had subclavian-pulmonary anastomosis: 126 of these have now been followed for 6 to 10 years, for an average of nearly 8 years; 10 (8 per cent) have died, 18 (14 per cent) have lost all or much of their improvement, but 98 (78 per cent) are as well or nearly as well as they were.

Good results maintained.—Most of these patients were children and, on the whole, they did best, but some adults did very well. The degree of improvement is illustrated by 2 boys: 1, aged 7, was enabled to lead a normal life at school except for games; after 10 years, he can walk 5 miles and get about the farm most of the day, but could not earn his living on a farm and is still a little cyanotic. The other, aged 13, has a normal color 10 years later and works in an accountant's office; for 2 years he had worked long hours in a garage, but found this too difficult.

Some patients included in the group with good results show obvious disability. A doctor seeing them for the first time would diagnose Fallot's tetralogy and might think they needed surgical treatment, and they would be better if their pulmonary blood flow had been increased even more than it has. However, it is difficult not to call the result good if a patient who could not walk 50 yards before operation can afterward earn his living and walk a mile, even if he shows obvious cyanosis and polycythemia. Many of them continue to be better in summer and can do less on cold days in winter. Apart from this, any suspicion of deterioration has generally been confirmed by the subsequent course.

Good results lost.—These patients have been divided into 2 groups: *(1)* those who have died, and *(2)* those who have lost all or much of their improvement. The loss is not always due to the closing of the anastomosis.

(1) In none of the 10 patients who died was there any evidence that the anastomosis had closed, and in 2 death was probably incidental—a man dying with carcinoma of the bronchus and a boy with a recurrence of nephritis. Cerebral abscess was the cause of 5 of the deaths, a very high incidence even though it is known to be common in tetralogy (9); 4 of these were particularly disappointing since they were in good

had averaged about half the systemic flows, were now nearly as high and in some cases higher. It has been suggested that successful direct operations would convert the condition into Eisenmenger's complex, and clearly in some of these the right-to-left shunt has been replaced by a left-to-right one, but the undeveloped outflow tract still provides enough resistance to prevent the pulmonary arterial pressure from rising above normal, and only 1 patient showed this and then only to 38/12 mm.

GOOD RESULTS LOST.—*Only 2 of the 79 patients have died, both from* incidental causes: 1 from acute ascending myelitis and the other from hydrocephalus due to an earlier basal meningitis.

Apart from these 2, only 2 others have lost all their improvement, but 5 have lost some of it. In these, the loss of ground must generally be due to increasingly severe stenosis, not always at the site of the operation. For example, 1 girl was greatly improved and could go dancing after a full day's work; her hemoglobin fell and her heart became larger. After 4 years, she had to give up her work, and catheterization showed that the gradient was now mainly infundibular. Clearly the operation had been incomplete, but her excellent condition for 3 years means that the infundibular stenosis must have become more severe, and at a subsequent operation the infundibulum was almost atresic. Generally, we think, the outflow tract steadily improves in capacity after a successful direct operation.

PULMONARY REGURGITATION.—Regurgitation has proved much less important after pulmonary than after aortic valvotomy, presumably because the relevant pressures are so much lower and the valve is rarely calcified. Pulmonary regurgitation occurred in 3 patients; in 2 it has not prevented a good result, though the heart is rather larger than usual; but in the third it was more severe and led to a very large heart and some congestive failure.

OBJECTIVE EFFECTS OF BOTH OPERATIONS

The success of these operations has been judged by the improvement in the patient's capacity and color, and these measure the essential changes. There is good correlation between this subjective judgement and the objective changes that follow and, except for the continuous murmurs, they apply equally to anastomotic and to direct operations.

PHYSICAL SIGNS.—An easily heard continuous murmur indicates a good flow through the anastomotic channel. If the former becomes hard to hear, the latter is probably smaller and is likely to close. The

health at their last follow-up, and yet died between the sixth and tenth years. Only 3 died of direct cardiac causes: 1 suddenly in the second year, and 1 with pulmonary edema on holiday in the fourth year; the third, who had been specially watched because her heart became unusually large after operation, remained well and acyanotic for 9 years but died with congestive failure in the tenth year.

(2) In 10 all improvement has been lost and in 8 others much of it. When the loss takes place fairly suddenly and the continuous murmur can no longer be heard, the reason is clear; in several patients, operation or necropsy has confirmed that the anastomosis had closed. But when the loss is gradual, it is more difficult to explain in this way; in some we think it may be due to a smaller flow through the anastomosis; in others, in whom the murmur is still well heard, to progressive stenosis. The anastomosis had closed in more than half of those who had lost all their improvement, and in all these the hemoglobin percentage had risen again, generally to its original level. Nearly always when this happens and the heart becomes smaller again, the anastomosis has closed.

SECOND OPERATIONS.—Of the patients who have lost their improvement, 10 have since undergone direct operations; results were excellent in 6, and 4 died. Direct operations after an earlier anastomotic one have proved difficult and the mortality is twice as high as for primary direct operations.

Results of Direct Operations

There have been many reports on the immediate results of pulmonary valvotomy and infundibular resection, but not many long follow-ups. We are therefore basing our conclusions on 111 patients operated on at Guy's Hospital by Sir Russell Brock, the total comprising those who had both infundibular resection and pulmonary valvotomy or either of these alone. Of the 111 patients, 79 (70 per cent) obtained good results, much the same proportion as after anastomotic operations. All the 79 have been traced for 2 to 9 years, with an average of 5 years.

GOOD RESULTS MAINTAINED.—Of the 79 patients, 70 (89 per cent) have remained well. Some who were very disabled can lead a quiet life with light sedentary work, but many are earning their living in more active employments and can also play games. The results of recatheterization in some of these confirm the clinical impression of the great improvement (14). The arterial oxygen saturation was always much higher and often over 90 per cent, and the pulmonary flows, which

to have an adequate pulmonary blood flow and is to lead a more active life. An increase of one-tenth in the cardiothoracic ratio when it was 45 per cent before operation leaves it of normal size and has no drawbacks, and when it was 50 per cent still leaves it only slightly enlarged. An increase to 55 or even 57 per cent does not seem harmful, but if it reaches 60 per cent we are more anxious; this, of course, happens more easily if the heart was large before operation.

Discussion

Many have reported their results after operation, but there are few series with long follow-ups. The report by White *et al.* (42) on the patients operated on by Taussig and associates is most valuable. Of the 212 with tetralogy of Fallot, 69 per cent have maintained their improvement for 5 to 8 years, 20 per cent have lost ground, and 11 per cent have died. The great value of a successful operation is shown by the contrast of this mortality figure with one of 44 per cent (8 of 18 patients) among those in whom the results were only fair. In our series *there is a similar contrast, with rates of 8 and 38 per cent, respectively.* Bacterial endocarditis occurred in 6 per cent of their 244 cases of congenital heart disease, but was rarely fatal. In our series, this complication has been less frequent, but cerebral abscess has been more common.

TABLE 2.—Results of Operations for Tetralogy of Fallot

Operation	Good Results		Subsequent Progress			Annual Loss (%)			
	Total No. Traced	Results Maintained	Died	All Improvement Lost	Much Improvement Lost	Died	All Improvement Lost	Much Improvement Lost	Total
Anastomotic .	126	98	10	10	8	1.0	1.0	0.8	2.8
Direct . .	79	70	2	2	5	0.5	0.5	1.4	2.4

Potts' aortopulmonary anastomoses.—The immediate results are similar to those after other anastomotic operations—an operative mortality of 9 per cent and a good result in 68 per cent. Potts *et al.* (35) have followed their first 100 cases and find that most good results have been maintained, at least as well as after other anastomoses; 5 patients had died. The heart generally seemed to increase in size rather more, but not progressively.

Comparison of anastomotic and direct operations.—No other follow-up study of a large series after direct operations has been found.

auscultatory signs are not much use after direct operations, and it is still possible to diagnose some stenosis in most successful cases.

SQUATTING.—When the result is good, the patient ceases to squat, and it is surprising that so long established a habit should be stopped so suddenly. Resumption of squatting always means that the patient has lost some and generally all of his improvement.

HEMOGLOBIN PERCENTAGE AND POLYCYTHEMIA.—A lasting fall toward normal in these measurements is generally a reliable sign of a better blood flow to the lungs and of less anoxemia. Any subsequent rise is generally a sign that the patient has lost ground. The mean hemoglobin of all our patients with good results fell from 130 to 103 per cent, and the fall was almost the same for anastomotic and for direct operations. The percentage was generally between 120 and 159 before operation and between 90 and 119 after it, though there was a wide range. Generally, this improvement has been maintained but sometimes the hemoglobin has risen above the lowest level to which it had fallen, rather more often after anastomotic than after direct operations. In 50 cases of the former, the average hemoglobin fell from 132 to 104 after 3 years and rose to 111 per cent after 8 years, perhaps only because the anastomosis failed to grow as much as the patient. In 20 cases after direct operations, it fell from 127 to 107 after 3 years and was still 106 after 7 years. A rise to near the original level is one of the most reliable signs that the patient is not doing well.

ELECTROCARDIOGRAM.—The ECG is not very useful in judging the result. The preponderance of the right ventricle is not likely to diminish, for it is still working against the same high pressure, and the increased activity must increase its work. As the years pass, signs of right ventricular strain increase in some patients, but so far they are not showing any harmful effects from this, though they may do so as time goes on.

INCREASE IN CARDIAC SIZE.—This was noticed almost at once after both operations, and at first there was some fear that it might be progressive and lead to heart failure. Generally, however, it reached its maximum a month or so after operation and has not been progressive. The average change in the cardiothoracic ratio was about one-tenth (from 49 to 53.5 per cent after 3 to 4 years and to 53 per cent after 8 to 10 years), and this is the same after anastomotic and after direct operation. These average figures hide large individual variation, and even in patients with very good results the increase may be less than this or much more.

In Fallot's tetralogy the heart is often small and undeveloped, partly from lack of use, so some increase must be expected if the patient is

disabled that they and their parents do not think much of the improvement. The condition, therefore, is one for which surgical treatment is still unsatisfactory.

TRICUSPID ATRESIA

INDICATIONS FOR OPERATION.—Nearly all patients with this are sufficiently disabled to need operation, and the outlook without it is much worse than that for Fallot's tetralogy. The only operation available is subclavian-pulmonary anastomosis.

OPERATIVE MORTALITY.—By chance, none of my 12 patients has died, but general mortality cannot be less than that for the tetralogy, i.e., about 5 per cent. Brown *et al.* (7) had 3 successive deaths after operation; all showed extensive pulmonary thrombosis, but this is not the general experience.

RESULTS OF OPERATION.—In my own series and in that of Taussig *et al.* (42), the results are less good than for the tetralogy, though most patients are better than they were and able to do more. It is, however, less likely to prove lasting, and only 2 of my 8 patients in whom the results were good are doing as well as the patients with tetralogy after 8 or 10 years. White *et al.* (42) also found a much higher mortality among this group in the series of Taussig and associates.

SUMMARY

The ideal operation for every congenital malformation should produce a complete cure, so that the patient can do what he wants with a normal expectation of life. This has, I think, been achieved for persistent ductus arteriosus but not for other cardiac conditions.

We can reasonably expect that this ideal will be achieved for the ostium secundum type of atrial septal defect, and also for simple pulmonary stenosis. We can reasonably hope that it will be for ventricular septal defects, if they are surgically treated in infancy or childhood, before the changes in the lungs have become irreversible.

Coarctation of the aorta can be vastly improved, but patients, and preferably children who have been operated on young, will need following for 20 years before we can speak of complete cure, and even then congenital bicuspid aortic valves may sometimes prove a drawback. Aortic stenosis can be relieved, but it is still uncertain to what degree the ideal of a good curative operation can be achieved.

Tetralogy of Fallot can be greatly improved, but another 10 years will be needed before we can have any right to talk of cure.

and it seems better to compare our own patients who have been assessed in the same way. It would have been a better comparison if they had been done alternately, but the anastomotic operations were done in 1947 to 1951 and the direct operations mostly in 1949 to 1952 but some up to 1956.

The results of both were very similar at first, but the longer the follow-up, the more favorable the results of the direct operations. Good results have been maintained in 89 per cent, and the annual death rate and the proportion losing all their improvement was only half those after anastomotic operations (Table 2).

FUTURE OUTLOOK.—Even after a successful operation, the tetralogy is still present, though in a slight rather than in a severe form. A larger proportion of patients should be able to lead a quiet life up to 40 or 50 years—a state one sees occasionally without operation. Assuming that the same proportion will continue to lose ground and that the mortality among these will continue high (38 per cent in 7 years), a rough forecast of the position after 7, 14, and 21 years can be made; 83 per cent should be alive and 64 per cent in good health after 14 years, and these figures should be 71 and 51 per cent respectively after 21 years. However, the average age will still be only about 31 years. Perhaps one-quarter will be able to carry on in this way until they are 50, but this is even more speculative. The proportion maintaining their good results after direct operations should become relatively higher as the years pass. The number of these patients who are able to work and enjoy life in a way that was impossible before is, however, even more important than the prolongation of life.

PULMONARY ATRESIA

INDICATIONS FOR OPERATION.—Most patients with pulmonary atresia are as disabled as those with severe tetralogy of Fallot—sufficiently so to make operation necessary if it is possible. Rarely is the atresia limited to the valve, in which case it could be helped by valvotomy; more often, it is long and fibrotic so that the only surgical treatment is subclavian-pulmonary anastomosis.

OPERATIVE MORTALITY.—This is much higher than similar operations for Fallot's tetralogy, about 20 per cent.

RESULTS.—The blood supply to the lungs already comes from the aorta through a persistent ductus or hypertrophied bronchial arteries; an anastomosis therefore does not help as much as in the tetralogy. In a few patients very good results have been obtained, but most have been only moderately improved and after some years they are so

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All surgeons realize the need for close cooperation with a physician in the selection of patients for operation. The importance of assessing the degree of improvement and its duration demands similar help in following patients for the next 30 years.

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Endocrinologic Factors in the Pathogenesis of Peptic Ulcer

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THE RECENT RENAISSANCE of interest in endocrinologic factors which may be of importance in the pathogenesis of peptic ulcer may be ascribed to at least three factors: *(1)* The more frequent clinical use of hormones which seem to have ulcerogenic properties, e.g., cortisone, has led to extensive studies on the effect of these hormones upon gastric secretion and peptic ulceration. *(2)* The common association of endocrinopathies, such as hyperparathyroidism, adenomatosis, and certain pancreatic tumors, with peptic ulcer has revived interest in the mechanisms responsible for the coexistence of these diseases. *(3)* The obvious fact that our basic knowledge and clinical management of peptic ulcer still leaves a great deal to be desired makes mandatory the investigation of any possible leads which might improve our understanding of peptic ulceration.

It is the purpose of this review to summarize current knowledge concerning hormonal influences on gastric activity and peptic ulceration, with emphasis placed on factors which recently have come into prominence. Previous extensive summaries (62, 90, 92) have systematically covered standard references on this subject, many of which will not be repeated in this review.

PITUITARY GLAND

The various anterior pituitary hormones which might be of importance in the pathogenesis of peptic ulceration are discussed in conjunction with the endocrine organs upon which they act.

(hypothalamus) by the enlarging pituitary tumor probably causes gastric hypersecretion and hyperperistalsis, rather than any effect the tumor itself might have in producing specific changes in the secretion of the stomach.

Experimentally, gastric ulcerations have been repeatedly produced in animals after the administration of pituitary extract (33, 31, 107, 111). It is generally held by investigators in this field that these ulcers are a result of the intense vasoconstrictive properties of the posterior pituitary substance, especially since only the pressor fraction but not the oxytocic principle produces this phenomenon. It is probable that the decreases in gastric secretion observed after the administration of posterior pituitary extract are a result of the local vasoconstriction within the stomach produced by this substance. Although Slutsky and coworkers (152) found a decrease in secretion in response to posterior pituitary substance, this material did not prevent the development of cincophen-induced ulcers in dogs. Dodds *et al.* (34), as well as Metz and Lackey (108, 109), also noted a decrease in gastric secretion after the administration of posterior pituitary extract. It should be mentioned, however, that Sandweiss and Saltzstein (136) found no protective effect of posterior pituitary substance on the development of Mann-Williamson ulcers in dogs, and Atkinson and Ivy (7) observed no effect of this drug upon canine Pavlov pouch secretion.

In summary, the pressor fraction of posterior pituitary extract exerts a potent vasoconstrictive effect upon the vessels of the stomach, an effect which may cause ulceration in experimental animals. There is apparently some associated decrease in gastric secretion. Despite these considerations, the drug has been disappointing in the treatment of human peptic ulceration. Changes in the function of the posterior pituitary in man are probably unimportant in the pathogenesis of peptic ulceration.

ADRENAL GLANDS

ADRENAL MEDULLA

Epinephrine may be of importance in the pathogenesis of peptic ulceration either through its action on the pituitary–adrenal axis, or by its direct activity on the stomach where it alters gastric blood flow and secretion.

Shay (147, 148) suggests that epinephrine produced in response to stress activates the hypothalamus, which in turn is important in producing "stress" ulcers. This concept has been seriously questioned by Wolfson (181), who has shown that epinephrine in physiologic amounts does not appreciably affect ACTH production.

Posterior Pituitary

The posterior pituitary does not occupy a particularly prominent place among the endocrine glands which have an effect upon peptic ulceration. However, the recent revival of the use of posterior pituitary substance (Pituitrin) in the treatment of bleeding esophageal varices (146) makes a review of the relation of the posterior pituitary gland to peptic ulceration seem appropriate, especially since portal hypertension has been shown to predispose to the ulcer diathesis (10).

Drouet (40), in 1933, was the first to advocate the use of posterior pituitary preparations for the treatment of peptic ulcers in man. Metz and Lackey (108, 109) later proposed the use of this material intranasally for patients with peptic ulceration, and cited their own experimental work demonstrating that the substance reduced the volume and acidity of gastric secretion. They suggested that hypofunction of the posterior pituitary might exist in patients with peptic ulcer, since many of these patients have nocturia and polyuria. Blotner's (20) finding that an increased volume and acidity of gastric juice was present in 6 patients with diabetes insipidus supports the suggestion of Metz and Lackey. Johnson *et al.* (82) have recently suggested, on the basis of experimental studies in dogs, that the rise in acidity and decrease in volume of gastric juice after section of the pituitary stalk was the result of deficiency of antidiuretic hormone. Administration of vasopressin restored gastric secretion to normal after pituitary stalk section. The over-all incidence of diabetes insipidus is so low, however, that it would be difficult to establish a definite relation between that disease and peptic ulcer in man. Kirsner (90), on the other hand, has seen no evidence of posterior pituitary deficiency in approximately 5,000 patients with peptic ulcer. The enthusiasm of Metz and Lackey for the use of Pituitrin in the treatment of peptic ulcer has not been shared by others (94), and it has not gained general acceptance for use in this disease.

The incidence of peptic ulceration among patients with pituitary tumors is probably no greater than that found in the general population (9). Wilson *et al.* (178) found peptic ulcers in only 5 patients of 512 with pituitary tumors (1 per cent), and in all 5 patients the peptic ulcer had preceded the development of the pituitary tumor by several years. Kirsner (90) found only one instance of coincidental duodenal ulcer and chromophobe adenoma of the pituitary in 6,200 autopsies. The ulcers associated with pituitary tumors have often been multiple, and are penetrating lesions closely resembling those seen with hypothalamic injury (12, 75). Irritation of the autonomic nervous system

After either physical or mental trauma, gastric secretion is temporarily diminished, followed shortly thereafter by hypersecretion of both acid and pepsin (41). Clinically, this is exemplified by the high incidence of reactivation of peptic ulcers in the postoperative or post-injury period (59). Such ulceration, in its most dramatic and lethal form, has been carefully documented by Hummel, Balikov, and Artz (78) and at the Brooke Army Medical Center, where 17 of 80 patients dying from extensive burns had severe peptic ulceration that was either the direct cause or an important contributing factor to the death of the patient. Observations such as those by Ellison *et al.* (50), emphasize the possible relation between stress, adrenal stimulation, and peptic ulcer. They have recently made the interesting observation in a study of 20,000 autopsies that adrenocortical hyperplasia was much more common in patients with gastroduodenal ulcer than in the general population.

Although the earlier work of Sandweiss and Saltzstein (136) suggested that stress ulcers were due to a deficiency of the gonadotropic hormone or of the adrenotropic hormone, later work seemed to indicate that ulceration following stress resulted from ACTH hypersecretion and adrenal stimulation. Based largely upon the experimental findings of Gray and co-workers (62, 65, 66), a number of workers have reported that chronic administration of either ACTH or cortisone leads to hypersecretion of both acid and pepsin and increased uropepsin levels (93, 186). ACTH was thought to be active only by its stimulation of the adrenal rather than by any direct effect on the gastric secretion, and it was felt that the action of cortisone was independent of either the gastric antrum or the vagus nerves. Unfortunately, many of these conclusions were based on uropepsin measurements, which are inaccurate indicators of gastric secretion. Moreover, the acute nature of many of the previous experiments and the inaccuracies of Levine tube collections of gastric juice make the results of these investigations somewhat doubtful. Some recent evidence suggests that neither ACTH nor cortisone appreciably increases gastric acid or pepsin secretion (42, 55, 106, 114).

However, even more current studies do not satisfactorily clarify the effect of cortisone upon gastric secretion. Wiederanders *et al.* (176), have been unable to demonstrate significant changes in secretion from vagally denervated pouches in dogs during prolonged administration of large doses of cortisone, and concluded that any variations in secretion which do occur are related to the dietary intake of the experimental animal. McGee (102), on the other hand, working in the same institution, demonstrated marked increases in Heidenhain pouch

Of more current interest is the action of epinephrine in altering gastric blood flow, with possible secondary changes in secretion of gastric juice. Epinephrine as a powerful vasoconstrictor diminishes gastric secretion (164). Peters and Womack (118) have shown that epinephrine produces gastric mucosal ischemia by diverting arterial blood into the portal bed via submucosal arteriovenous shunts. Such a diminution in gastric secretion produced by epinephrine is operative despite hypoglycemia, peptone, or histamine stimulation (60, 99). The latter findings in man do not apply to the dog (87) or the cat (101).

Palmer and Sherman (117), in a recent review, have postulated that hypoxia of the gastroduodenal mucosa may be the final common pathway of peptic ulceration, subsequent either to a plethoric engorgement or ischemia of the stomach wall. Obviously, epinephrine is only one of several factors which might control the vascular supply to the gastroduodenal mucosa through its effect upon submucosal gastroduodenal arteriovenous shunts.

In all of the studies cited, epinephrine as a powerful splanchnic vasoconstrictor was found to be the more active gastric secretory depressant than norepinephrine (4).

These recent studies on the effect of epinephrine on gastric blood supply and, in particular, on the possible importance of submucosal arteriovenous shunts are, of course, a revival of interest in a subject that for a number of years dominated thinking in regards the pathogenesis of peptic ulcer (36). Perhaps the newer approaches will be more fruitful, for our own laboratory experience suggests that gastroenteric mucosal blood supply is under second-to-second variation via arteriovenous shunts and can be altered by numerous factors.

Adrenal Cortex

Selye's concept of stress as a factor in the pathogenesis of disease has been extensively applied to explain peptic ulceration, and a huge literature has appeared during the past 15 years on the relation of adrenocortical stimulation to gastric hyperactivity. According to this concept, stress provokes a release of ACTH from the pituitary, which in turn causes the release of corticosteroids from the adrenal. Since peptic ulceration is known to occur after such nonspecific stress as severe burns (Curling's ulcer), it was easy to assume that steroids stimulate gastric secretion and thus produce peptic ulceration. It is now becoming increasingly obvious, however, that this attractively simple explanation does not completely explain the relation between adrenocortical activity and peptic ulceration.

After either physical or mental trauma, gastric secretion is temporarily diminished, followed shortly thereafter by hypersecretion of both acid and pepsin (41). Clinically, this is exemplified by the high incidence of reactivation of peptic ulcers in the postoperative or post-injury period (59). Such ulceration, in its most dramatic and lethal form, has been carefully documented by Hummel, Balikov, and Artz (78) and at the Brooke Army Medical Center, where 17 of 80 patients dying from extensive burns had severe peptic ulceration that was either the direct cause or an important contributing factor to the death of the patient. Observations such as those by Ellison *et al.* (50), emphasize the possible relation between stress, adrenal stimulation, and peptic ulcer. They have recently made the interesting observation in a study of 20,000 autopsies that adrenocortical hyperplasia was much more common in patients with gastroduodenal ulcer than in the general population.

Although the earlier work of Sandweiss and Saltzstein (136) suggested that stress ulcers were due to a deficiency of the gonadotropic hormone or of the adrenotropic hormone, later work seemed to indicate that ulceration following stress resulted from ACTH hypersecretion and adrenal stimulation. Based largely upon the experimental findings of Gray and co-workers (62, 65, 66), a number of workers have reported that chronic administration of either ACTH or cortisone leads to hypersecretion of both acid and pepsin and increased uropepsin levels (93, 186). ACTH was thought to be active only by its stimulation of the adrenal rather than by any direct effect on the gastric secretion, and it was felt that the action of cortisone was independent of either the gastric antrum or the vagus nerves. Unfortunately, many of these conclusions were based on uropepsin measurements, which are inaccurate indicators of gastric secretion. Moreover, the acute nature of many of the previous experiments and the inaccuracies of Levine tube collections of gastric juice make the results of these investigations somewhat doubtful. Some recent evidence suggests that neither ACTH nor cortisone appreciably increases gastric acid or pepsin secretion (42, 55, 106, 114).

However, even more current studies do not satisfactorily clarify the effect of cortisone upon gastric secretion. Wiederanders *et al.* (176), have been unable to demonstrate significant changes in secretion from vagally denervated pouches in dogs during prolonged administration of large doses of cortisone, and concluded that any variations in secretion which do occur are related to the dietary intake of the experimental animal. McGee (102), on the other hand, working in the same institution, demonstrated marked increases in Heidenhain pouch

secretion during administration of massive doses of cortisone. He also observed that resection of the antrum abolished the secretory response of the pouch to the cortisone. It is obvious that many more carefully controlled studies are necessary to evaluate properly the effect of cortisone upon gastric secretion.

If adrenocortical stimulation by ACTH or the administration of cortisone produces peptic ulcer, marked adrenal hyperfunction might be expected to cause a high incidence of ulcer, yet Cushing's disease is not so characterized. On the other hand, during acute adrenal insufficiency, multiple gastric erosions with reduced gastric secretion may occur, both of which respond to corticoid replacement therapy (159). A similar decrease in both acid and pepsin secretion has been noted in adrenalectomized rats (2). In dogs, ACTH does not restore the depressed gastric secretory activity following adrenalectomy, indicating that the activity of this hormone on the stomach depends on its effect on the adrenal gland (171). Saegesser (131) presents evidence to the contrary in this regard, however.

At the present time, the anti-inflammatory effect of corticoids are being emphasized as of possible importance in the causation of peptic ulceration. According to this theory, pre-existing ulceration or new erosions may fail to heal due to inhibition of the tissue inflammatory responses (124, 139, 177).

In the Shay rat, the anticipated gastric ulcers following ligation of the pylorus do not develop in previously adrenalectomized rats (71) but do develop when corticoid replacement therapy is given (103). The Shay rat has been suggested as an appropriate biologic means of measuring both the ulcerogenic and anti-inflammatory properties of corticosteroids, since moderate amounts of steroids may on the one hand minimize the inflammatory response to ulcers in the ruminal portion of the stomach while promoting ulceration in the gastric corpus (124).

Whatever the mechanism (and its exact definition is not yet clear), there is ample evidence that the use of either ACTH or corticosteroids unfortunately will activate peptic ulceration. Sandweiss (134) collected 50 such cases in 1954, and in the ensuing 5 years a literal flood of confirming case reports have appeared. In general, it is felt that corticoids most probably only reactivate pre-existing ulcers (89, 134), a difficult hypothesis to disprove since its refutation necessitates proof that no ulcer existed before steroid administration. Small doses of steroids, i.e., less than 50 mg. cortisone a day, or short courses of the drug, are much less likely to cause ulcer symptoms than more prolonged administration (89, 134). The extensive and often indiscrimi-

nate use of steroids at the present time, unfortunately, offers evidence of the ulcerogenic properties of these drugs. Before corticosteroids are administered, a careful history must be obtained to ascertain the possibility of a previously existing peptic ulcer. If such is the case and corticoid therapy is absolutely mandatory, prophylactic treatment of the ulcer should probably be undertaken at the same time. Even under such circumstances, a high incidence of ulcer reactivation must be anticipated. In the presence of active peptic ulceration, corticoid therapy is probably extremely dangerous.

Gonads

No important contributions have been made recently referable to the relation between the gonads or their pituitary tropic hormones and peptic ulceration. A review of available information on this subject may serve to redirect our attention to this area of thought, with the possibility that many of the unsolved problems in this regard might be solved in the future.

There is no question that peptic ulceration is more common in adult men than in adult women. Gastric ulcer is three to four times more frequent and duodenal ulcer approximately ten times more common among adult men than women (79, 163). The importance of this difference in incidence of peptic ulceration among adults is all the more striking in view of the fact that before puberty peptic ulcer is equally common to the two sexes and after the menopause the incidence of ulcer in women rises (90, 179). The reasons are not known at present; whether or not androgenic hormones increase the ulcer diathesis remains to be determined.

Peptic ulcer is quite rare during pregnancy (83, 138). Moreover, Szenes (162) has reported marked improvement in pre-existing ulcers when gestation occurred. It is interesting that although amelioration of peptic ulceration often occurs early in pregnancy, complications of ulcer when they do appear seem to have a predilection for the last trimester or the immediate postpartum period (16, 21, 110, 140). These findings correlate closely with the changes in gastric secretion observed during pregnancy. Strauss and Castle (160) noted that gastric secretion diminished during the first two trimesters of pregnancy but increased during the last month of gestation. Others have also observed that the gastric secretion decreased during the first and second trimesters (6, 162). It has been suggested that fluctuations in chorionic gonadotropins might be responsible for the changes in gastric secretion during pregnancy. Sandweiss and Saltzstein (136) noted that the ad-

ministration of either follicle-stimulating hormone or luteinizing hormone are of value in the healing of experimental Mann-Williamson ulcers. This finding correlates nicely with Way's (173) observation that the decreased gastric secretion during early pregnancy occurs when gonadotropin levels are extremely high, whereas the increased gastric acidity late in pregnancy develops at a time when gonadotropin levels are on the decline. It may be that adrenal activation late in pregnancy is an additive factor in causing activation of ulcers during this stage of gestation (170).

Information, however, on the effect of menstruation upon peptic ulceration is meagre. Hellebrandt and Brogdon (73) have found some decrease in gastric secretion during menstruation and have suggested that progesterone might be the responsible factor. Progesterone has also been observed to have an ameliorating effect upon experimental Mann-Williamson ulcers (136). Clinically, however, there is no consistent effect of menstruation upon the symptoms of peptic ulcer (76).

Estrogens have been given extensive trial in the treatment of peptic ulcer. Although many reports have indicated favorable results (95, 115, 145), these can be seriously questioned because of the poorly controlled manner in which these studies were carried out. The concomitant use of other means of treatment of peptic ulcer could also easily account for the relief of symptoms noted in these reports. Other studies have indicated that recurrences are frequent when estrogens are used (142, 179). Some of the beneficial effects of estrogen therapy for peptic ulcer have been ascribed to gastric hyperemia, but this has by no means been proved. No definitive studies have been carried out to ascertain whether or not estrogens increase the resistance of the duodenal or gastric mucosa to ulceration. Most investigators have found that estrogens do not significantly decrease gastric secretion in patients with peptic ulcer (5, 80, 90). In fact, Abrahamson and Hinton (1) have observed an increased secretory response to histamine after the administration of Theelin to patients with duodenal ulcer. Mention should be made of the fact that Kirsner (90) also noted no definite effect of progesterone upon gastric secretion.

Administration of chorionic gonadotropin has not produced consistently good results in the treatment of peptic ulcer in man (135, 137). Nor has this substance been shown to decrease gastric secretion with any regularity (57, 90, 138).

It must be concluded that although there are striking differences in the sex incidence of peptic ulcer we are as yet unaware of the reasons for it. The ameliorating effect of early pregnancy upon peptic ulceration does not clarify the hormonal mechanisms which might be re-

sponsible for sex differences in the incidence of peptic ulceration. Estrogens and chorionic gonadotropin do not consistently alter gastric secretion or affect the clinical course of human peptic ulceration. There is no really convincing evidence available to suggest that these substances significantly improve the resistance of the gastroduodenal mucosa to peptic ulceration.

PARATHYROID GLANDS

Hypoparathyroidism

Peptic ulceration occurs infrequently in patients with hypoparathyroidism. In a detailed study of 52 patients with idiopathic hypoparathyroidism, Steinberg and Waldron (157) did not find a single instance of peptic ulcer; they cite a personal communication from Howard, Reifenstein, and Sprague confirming the infrequency of the coexistence of these two diseases. The tetany occasionally found in patients with prolonged gastric obstruction due to chronic duodenal ulcer is caused by the metabolic alkalosis secondary to prolonged vomiting rather than hypoparathyroidism.

Analysis of patients with uncomplicated peptic ulceration likewise reveals that the serum calcium is normal (158). It should be noted, however, that Grove and Vines (69) recommended parathyroid extract for the treatment of peptic ulcer after finding hypocalcemia in 12 patients with ulcer. Others have found this therapy ineffective, however (100). Kirsner (90) stated that injection of parathormone only occasionally diminished basal gastric secretion of man. Although the report of Grove and Vines led to considerable speculation about the relation between hypoparathyroidism and peptic ulcer, it is now generally conceded that no important connection exists between these two diseases.

The effect of experimental parathyroidectomy on gastric secretion has been extremely variable. Keeton (88) reported a decrease in volume, free and total acidity, and digestive power of the gastric juice after removal of the parathyroid glands. On the other hand, Schiffrin (141) and Lebedinskaia (97) noted increased secretion in dogs after parathyroidectomy. Many of these studies were performed on a few animals only, and certainly more thorough investigations using modern technics under carefully controlled conditions are necessary to clarify these conflicting findings.

Hyperparathyroidism

Although Gutman *et al.* (70) pointed out the frequency of gastrointestinal symptoms in hyperparathyroidism in 1934, Rogers (127)

was the first to call attention in 1946 to the association between hyperparathyroidism and peptic ulceration in a report of 2 cases, one caused by a parathyroid adenoma and the other by hyperplasia of the parathyroids. Treatment of the peptic ulcer by the usual means caused exacerbation of the hyperparathyroidism, with symptoms of severe parathyroid poisoning. The correct diagnosis was not made until postmortem examination. Shortly thereafter, Rogers *et al.* (128, 129) reported 3 more cases of parathyroid hyperplasia, 2 of which had peptic ulceration. Berlin (15) reported a single case of parathyroid hyperplasia associated with duodenal and esophageal ulceration found at autopsy in 1949.

Two years later, Schneider and Robenett (144) vividly pointed out the association of these two diseases in a report on a patient with hyperparathyroidism without skeletal or renal disease. The primary symptomatology was that of unrelenting peptic ulceration. Removal of a parathyroid adenoma resulted in complete relief of the peptic ulcer. Since then, several others have recorded cases in which peptic ulceration was a prime complaint and in which surgical treatment of the hyperparathyroidism was followed by complete remission of the peptic ulceration (3, 132, 143, 167). The relief of the ulceration after treatment of the hyperparathyroidism is strongly suggestive of a clear-cut relation between these two diseases.

An analysis of the larger series of cases of hyperparathyroidism reported in the literature confirms the association suggested by these sporadic case reports. Black (19) notes that 24 per cent of the patients with hyperparathyroidism in the Mayo Clinic series had proved peptic ulcers and an additional 15 to 20 per cent had ulcer-like symptoms without definite proof of ulceration. Most of the ulcers were duodenal in location, although a few gastric ulcers were also present. Of the Johns Hopkins group of patients with hyperparathyroidism, 15 per cent had gastroduodenal ulcers (77). In Hellstrom's (74) series of 50 patients, 14 per cent had peptic ulcers, all of which were duodenal in location. St. Goar (132, 133) found approximately a 9 per cent incidence of peptic ulceration in two different series of patients with hyperparathyroidism, but not all of the patients with ulcer-like symptoms had had roentgenographic examinations of the stomach and duodenum. The above figures are greater than the 5 to 10 per cent incidence of peptic ulcer found among the general population in this country (91). Whether or not hyperparathyroidism is more frequent in patients with peptic ulcer than in the general population is unknown, and will require investigation of very large numbers of patients with peptic ulcer. Preliminary investigations in our own insti-

tution have been unproductive as yet in uncovering unsuspected hyperparathyroidism in a relatively small group of patients with peptic ulcer.

The mechanism responsible for the peptic ulceration associated with hyperparathyroidism has not been clearly elucidated. One of the first possibilities which comes to mind is that the parathyroid glands might exert some effect upon gastric secretion. The available experimental and clinical evidence in this regard is rather spotty, conflicting, and inconclusive, although the predominant opinion is that the changes in gastric secretion occurring in hyperparathyroidism are not great enough or in the proper direction to cause peptic ulceration. Babkin *et al.* (8) and Grant (61) have demonstrated that secretion from Pavlov (vagally innervated) pouches generally diminishes in proportion to rises in serum calcium evoked by the administration of activated ergosterol, parathormone, or calcium salts. *In vitro* studies of frog gastric mucosa by Gray and Adkison (63) also showed that either decreasing or increasing the calcium content of the test medium resulted in a decrease of acid secretion. Shiffrin (141) found that the volume and acidity of Pavlov pouch secretion decreased, whereas that from a Heidenhain pouch increased when irradiated ergosterol or parathyroid extract were administered. On the other hand, these drugs caused an increase in pepsin concentration in the dogs with Pavlov pouches but no change in pepsin in the case of the Heidenhain pouch. In our own laboratory, no consistent changes in magnitude of secretion from either Heidenhain or Pavlov pouches occurred during or after the administration of parathormone or vitamin D (149).

Clinically, Kirsner (91) has not observed any direct correlation between gastric secretion and parathyroid activity. Howard *et al.* (77) made the surprising observation that the gastric secretion was diminished in their patient at the height of ulcer activity during the hyperparathyroid state. When the hyperparathyroidism was corrected surgically, the ulcer symptoms disappeared and the gastric acidity rose.

In summary, it is apparent that although experimental studies are somewhat inconclusive, the secretion of gastric juice generally diminishes when parathormone, vitamin D, or calcium salts are given. On the basis of the experimental and meagre clinical data, hypersecretion of acid is probably not an important etiologic factor in the ulcer of hyperparathyroidism. Certainly more careful *clinical* investigation of hyperparathyroid patients with and without peptic ulcer is necessary. The changes in pepsin concentration reported by Schiffrin (141) are interesting but cannot be completely assessed at the present time.

Aside from changes in acidity, hyperparathyroidism might con-

ceivably cause local changes within the gastric or duodenal wall which might predispose to the development of peptic ulceration. Repeated injections of parathyroid extract or calcium salts into dogs have produced intense hyperemia, congestion, and necrosis in the stomach and small intestine (24, 31). It has been suggested that parathyroid extract might cause breakdown of the mucoprotein of the gastrointestinal tract, rendering it more susceptible to ulceration (52). Arteriosclerosis of the vessels within the upper gastrointestinal tract has also been suggested as a possible cause for the peptic ulceration in hyperparathyroidism (47). Further investigation of local changes predisposing to peptic ulceration is necessary.

The frequent association of hyperparathyroidism with multiple endocrine adenomas may in some way serve to augment the ulcerogenic tendencies in this disease. Many have reported the common finding of multiple endocrine adenomas (16, 46, 48, 58, 168), but the relative importance of each endocrine gland which is involved has not been ascertained.

Wermer (173, 174) has called attention to the possibility that genetic factors may play a role. Characterization of this genetic factor has not been accomplished.

The question has been raised whether the prolonged ingestion of milk and alkali for the treatment of duodenal ulcer might cause hyperactivity of the parathyroid glands. St. Goar (132) pointed out, however, that there was no specific correlation between the onset of hyperparathyroidism and the type and duration of alkali therapy. Moreover, intake of large quantities of absorbable alkali depress the activity of the parathyroid glands (90). It would seem, therefore, that although the "milk-alkali syndrome" may be extremely difficult to differentiate from hyperparathyroidism (96), the prolonged treatment of peptic ulcer with milk and alkali probably does not cause hyperparathyroidism.

In conclusion, there seems to be little question that there is a definite relation between peptic ulceration and hyperparathyroidism. The pathogenesis of these ulcers is unknown, although a combination of many of the factors just mentioned might be responsible. Patients having peptic ulceration resistant to medical or surgical therapy should be investigated for the possible presence of hyperparathyroidism. Children or young women with duodenal ulcer should be especially suspect. More careful clinical investigation of gastric secretory activity in patients with hyperparathyroidism might provide a clue to the pathogenesis of peptic ulceration in this disease. It is unfortunate that the diagnosis of hyperparathyroidism so often and so completely depends

on laboratory determinations. It is possible that as more sensitive and accurate methods of determining the serum calcium are developed, more cases of relatively early stages of hyperparathyroidism will be discovered among patients with peptic ulceration.

PANCREAS

The pancreas has been implicated in the pathogenesis of peptic ulceration either experimentally or clinically in one of the following ways: *(1)* by experimental diversion of its alkaline juices away from the gastrointestinal tract; *(2)* by production of hyperinsulinism and hypoglycemia; or *(3)* by an ulcerogenic pancreatic hormone not related to insulin. Each possibility has been receiving its share of clinical and experimental interest in the immediate past.

When the protective alkalinizing pancreatic juice is removed from the upper gastrointestinal tract by pancreatic duct ligation (51, 120), by an external fistula (35), or by diversion into a lower portion of the intestinal tract (104), a high instance of peptic ulceration results. The last-mentioned procedure is the basis for the Mann-Williamson dog which has been extensively used for the production of ulcer in the experimental animal. All of these procedures, of course, have no relation to the endocrine function of the pancreas, and therefore no further discussion of them is warranted in this review.

Experimental hyperinsulinism will produce hypoglycemia and will result in increased hunger contractions and gastric motility (23). For a number of years it was assumed, largely on the basis of animal studies, that insulin-producing tumors of the pancreas were associated with a high incidence of peptic ulceration. More recent clinical studies (81) suggest that no such correlation exists. Poth and associates (121) administered insulin to dogs for a long time and produced peptic ulceration, but thought that the effect might be due to a substance in the commercial preparation other than insulin. They further suggested that hypoglycemia does not produce ulceration in man.

It has long been thought that peptic ulceration develops infrequently in diabetics. An ulcer incidence of 0.25 per cent (130) and 0.78 per cent (182) has been reported in two large series of diabetic patients. Furthermore, Ivy *et al.* (80) have pointed out that achlorhydria is found in diabetics with greater frequency than in the normal population. Recently, however, Ellison and co-workers (50), in a review of 20,000 autopsies, have found a 7.4 per cent incidence of gastroduodenal ulceration among 500 cases of diabetes. This is at least as common as the incidence of ulceration in the general population.

Poth and co-workers (119, 121) were the first to suggest, in 1950, that a pancreatic hormone other than insulin might have ulcerogenic properties and that the hyperglycemic factor glucagon might be the responsible agent. This hormone, which arises from the alpha cells of the pancreatic islets (13), has excited tremendous clinical and experimental interest (169) during the past decade, and quite logically its effect on gastric secretion has been investigated. Stunkard and co-workers (161) have shown that glucagon decreases gastric motility, and Robinson *et al.* (126) that glucagon decreases gastric secretion. Earle (44) has similarly demonstrated a decrease in blood pepsinogen following glucagon administration. All of this evidence casts serious doubt upon the suggestion that glucagon possesses ulcerogenic properties, since each of its physiologic activities seems to produce an effect opposite to that which would be anticipated from ulcerogenic substance.

In 1955, Zollinger and Ellison (185) gathered a number of cases of their own as well as several from previously published series in which fulminating, resistant peptic ulceration of the stomach, duodenum, and jejunum associated with profound gastric hypersecretion was found in conjunction with a noninsulin producing tumor of the islet cells. They suggested for the first time that such alpha cell tumors might produce an ulcerogenic hormone. Since that time more than 70 similar cases have been reported (46, 51), and the Zollinger-Ellison syndrome has been more clearly defined.

The triad of a fulminating ulcer unresponsive to treatment, gastric hypersecretion, and a nonbeta cell islet tumor remains the key to the syndrome, but it is now recognized that about half of the cases are associated with adenomas of other endocrine glands. The parathyroid, adrenal cortex, pituitary, and even the other cells of the islets of Langerhans have all been found to be the site of adenomas, in addition to the adenoma of the alpha cells of the pancreatic islets. Whereas at first it was thought that these tumors were only of the alpha cells, it is now evident that any of the islet cells other than the beta cells may be involved. In many cases the pancreatic adenomas are multiple and are predominately located in the body and tail of the pancreas (48, 185). Follow-up of the cases now makes it apparent that essentially all of these tumors are of a low-grade malignancy with a propensity for metastasis to the liver (185).

The mechanism by which these tumors assert their ulcerogenic effect remains obscure. The original hypothesis that glucagon was being secreted by these tumors no longer seems tenable, for the reasons mentioned above. Jones (84) suggests that the tumors may me-

chanically block the gastric outlet; this hypothesis seems unlikely in view of the absence of this finding in the large number of reported cases. The causative relation between these pancreatic tumors and the fulminating peptic ulceration associated with them has recently been questioned, mainly because the value of pancreatectomy in protecting against the recurrent ulceration in reported cases seems doubtful and because of the extremely frequent occurrence of multiple endocrine adenomas in these patients (175).

Practically, the clinician should suspect this tumor in any particularly persistent peptic ulceration that will not respond to the usual forms of medical and surgical therapy. Clinical suspicion should be particularly high if other endocrine adenomas are present, or when the ulceration is found in an unusual location such as the jejunum.

The exact therapeutic path to be taken in these cases is as yet unclear, for the natural history of the disease is only now unfolding. If at the time of laparotomy the surgeon suspects such a tumor, he should perform a thorough exploration of the pancreas with careful visualization and palpation of that organ. When his clinical suspicion is extremely high (and most reported cases have had numerous previous operative procedures in an effort to eradicate the ulcer diathesis), the surgeon might excise the entire body and tail of the pancreas so that the pathologist can determine by more careful section whether such an adenoma is present.

If a tumor is found, it should be frozen immediately for subsequent experimental biologic assay for ulcerogenic properties, for only by this means will any endocrine effects be established. Since most, if not all, of these tumors are malignant, the lesion should be excised widely and precautions taken to include any other palpable masses in the pancreas. Because the gastric ulceration is of such a persistent nature and because small metastases as well as multiple tumors might well perpetuate the ulceration, Zollinger and McPherson (185) advocate total gastrectomy whenever the tumor is discovered. They report 1 case, however, in which removal of the primary pancreatic tumor resulted in a marked reduction of the previously huge quantities of gastric secretion after subtotal gastrectomy and vagotomy had failed to influence the output of acid.

GASTROINTESTINAL TRACT

We will discuss here only those aspects of the influence of gastrointestinal hormones upon peptic ulceration in which recent important advances have been made.

Gastric Antrum

Gastric secretory stimulating hormone (gastrin).—The classic description of the antral hormone by Edkins (45) in 1905 and the subsequent fundamental work on this substance is too well known to require review. Recent interest has centered about what stimuli cause the secretion of gastrin and what factors inhibit its production. A great deal of investigation has also recently been carried out on whether or not the antrum actually secretes a hormone which inhibits gastric secretory activity. Studies by Baugh and co-workers (12) indicate that gastrin arises in the mucosa and submucosa of the antrum in the neighborhood of Meissner's plexus. This hormone (gastrin) apparently acts directly on the parietal cells.

The release of gastrin is stimulated by distention of the gastric antrum, by meat and protein breakdown products, by alcohol, and by alkaline substances in contact with the antral mucosa (67). Dragstedt and co-workers (38) devised an antral pouch which they attached to the colon where it was in continual contact with the fecal stream. Not only did marked increases in Heidenhain pouch (vagally denervated) secretion occur, but also severe peptic ulceration developed in many of their animals. The same phenomenon, to a slightly lesser degree, occurred when the antral pouch was attached to the duodenum or jejunum. Such hypersecretion does not occur when the antral pouch is removed from intestinal continuity (39). This superb series of experiments has led Dragstedt to postulate that human gastric ulcers might be caused by hypersecretion of hormonal origin (antrum), whereas duodenal ulcers arise as a result of hypersecretion of vagal origin. Whether or not this hypothesis is correct will require much study in the human subject. This study, however, will be seriously hampered by difficulties arising from the lack of a completely suitable test of antral function. Evidence that alkalinity of the antral content is a stimulus to gastric acid secretion is furnished by the frequent occurrence of ulceration following the Finsterer antral exclusion operation, after which alkaline duodenal contents constantly bathe the otherwise empty gastric antrum (80). Similarly, the diminution of gastric acid following vagotomy or fundic resection produces an excessive secretion of gastrin and results in an increased Heidenhain pouch secretion in dogs (54). Of course, some of the Heidenhain pouch hypersecretion after vagotomy also results from antral stasis secondary to the pylorospasm induced by section of the vagus nerves.

These experimental findings make it evident that alkaline juice or mechanical distention stimulates the antrum to produce gastrin, thereby stimulating acid secretion. Similar data has been accumulated

to show that acid applied either to an isolated antral pouch or to the antrum in place diminishes gastric secretion (113, 183). This inhibitory action of acid is of importance in the surgical placement of a *gastroenterostomy stoma, which should be as close as possible to the* pylorus so that the acid gastric juice is not entirely diverted from the antrum. Placement of the gastroenterostomy close to the pylorus also assures good antral drainage.

Failure to accomplish adequate antral drainage would give rise to antral stasis with subsequent release of gastrin, which in turn stimulates gastric secretion.

GASTRIC SECRETORY INHIBITING HORMONE.—There is currently a growing feeling among gastric physiologists that the antrum secretes a second hormone which actively inhibits gastric secretion (28, 105). Since several substances inhibit the release of gastrin from the antrum, the question obviously arises whether such a gastric secretory inhibition results from a separate and distinct inhibitor hormone or is merely the result of a reduced production of gastrin.

A part of the confusion is due to lack of knowledge of the exact method by which gastrin stimulates the release of gastric acid. According to the work of Quigley and Louckes (122), gastrin acts via nervous control, for the hormone's activity can be blocked not only by local anesthetic agents placed upon the antral mucosa but also by atropinization or ganglionic blocking agents.

The best evidence that the antrum does indeed secrete a separate gastric inhibiting hormone comes from study of separated antral pouches. Harrison and associates (72), in 1956, implanted one-half of the antrum into the colon as a diverticulum similar to those used in the experiments of Dragstedt. The remaining half of the antrum was left in continuity with the gastrointestinal tract and anastomosed to the duodenum. After base-line secretions from a previously constructed Heidenhain pouch were obtained, the antral segment in continuity with the duodenum was excised. Upon removing the inhibitory effect of the antral remnant attached to the stomach, gastric hypersecretion resulted, thus indicating that this segment of antrum actively inhibited secretion from a denervated pouch. An even more elegant experimental preparation has been devised by Jordan and Sand (86) who prepared two separate antral pouches in Heidenhain pouch dogs and showed that *acid introduced into one pouch inhibited the secretagogue* action of alcohol or histamine in the other. Margolus and Harrison (105) have also demonstrated the inhibitory action of the antrum upon the intestinal phase of gastric secretion by showing a decrease in secretion from Heidenhain pouches in response to a meal while an isolated antral pouch is perfused with 0.1N hydrochloric acid.

Whether this inhibitory action on secretion is transmitted via the vagus or sympathetic nerves or whether it is solely a humoral phenomenon is still not clear. Grossman (68) showed that histamine-induced secretion from vagally denervated total gastric pouches is inhibited by retching and nausea induced by an inflated tube placed in the region of the esophagoduodenal anastomosis. This inhibition occurs even after abdominal splanchnicectomy and lumbar sympathectomy. He concluded that the marked inhibitory effect of the nausea and vomiting were independent of neural connections. Code and Watkinson (29) believe that such inhibition is mediated via vagal fibers. State and Morgenstern (156), on the other hand, believe that the antrum definitely produces an inhibitory hormone not dependent on vagal innervation, since perfusion of a completely isolated antral pouch with 0.1N hydrochloric acid inhibited the secretory response of a Pavlov pouch to the ingestion of a meal. Complete confirmation of this thesis, however, will require repetition of these experiments with antral and indicator pouches transplanted to the subcutaneous tissue to ensure complete vagal denervation.

The nerve supply to the antrum has received increasing attention recently, and experimental studies have demonstrated its importance for antral hormonal activities. Oberhelman *et al.* (112) have shown that so long as the antrum remains innervated antral phase gastric secretion continues unabated even when the antrum is totally isolated from gastrointestinal continuity. They concluded that antral motility is adequate stimulus for antral phase secretion. On the other hand, Wohlrabe and Kelly (180) have demonstrated that although vagal denervation of the isolated antrum reduces the total daily secretion from a Heidenhain pouch, antral response to a chemical stimulus is not significantly altered by division of its vagal nerve supply. Jones, DeVito, and co-workers (85) have pointed out the importance of intrinsic antral innervation by demonstrating that interruption of the continuity between the mucosal and muscular layers of the stomach, an operation they termed antroneurolysis, seriously impairs the normal function of the antrum. They have further demonstrated that antroneurolysis reduces the influences normally mediated by the myenteric plexuses, so that the threshold of the antrum to normal stimuli which cause the production of gastrin is raised (32).

Another new field of investigation has been thrown open by the recent demonstration by Ragins and colleagues (123) that intravenous administration of antihistaminic agents abolishes the antral phase of secretion. This is particularly noteworthy in view of the fact that antihistaminic agents do not alter the effect of histamine upon gastric

secretion. The mechanisms responsible for this phenomenon are not clear but certainly merit further investigation.

Intestinal Hormones

The intestinal phase of gastric secretion has generally been regarded as of far less importance than either the cephalic or gastric phases. Dragstedt *et al.* (39), for example, have estimated that the cephalic and antral phase each account for 45 per cent of gastric secretory activity, whereas the intestinal phase is responsible for only 10 per cent. Classically, the intestinal phase results from the entrance of the products of gastric digestion into the duodenum. Whether these products themselves act as gastric secretagogues when absorbed into the blood stream or whether they cause the release of a hormone from the intestinal mucosa has never been clearly elucidated.

Recently, marked increases in secretion from canine Heidenhain pouches have been observed after partial constriction of the portal vein (66), following the creation of an Eck fistula (43), or after portacaval transposition (25, 26, 150). The importance of these interesting observations is immediately apparent, since peptic ulceration is not only common in patients with cirrhosis of the liver, but is also frequent after portacaval shunts (26). Recent studies in our own laboratory (150), as well as those by Clarke and associates (27), have strongly suggested that the hypersecretion after portacaval shunts results from an unmasking of the intestinal phase of gastric secretion. Hepatic bypass of intestinal blood apparently allows a secretagogue released by the intestine to act upon the stomach without being altered by the liver. Preliminary experiments in our laboratory have suggested that histamine is the humoral agent in question, but more extensive investigations are necessary to confirm this hypothesis. The hypersecretion noted after portacaval transposition is largely abolished by fasting (5, 26), but is unaffected by antrectomy (26) or vagotomy (38). We have shown that the protein component of the diet is largely responsible for the hypersecretion.

These experiments have opened new vistas in the study of peptic ulceration, and further elucidation of the causes for these findings will most certainly provide better understanding of some of the more basic aspects of gastric secretion.

Carcinoid Tumors

For many years carcinoid tumors of the gastrointestinal tract have been known and described by pathologists but have excited little in-

terest. In 1953, Lembeck (98) first noted that such a tumor contained large amounts of 5-hydroxytryptamine (serotonin). Classification of this neoplasm as a hormone-producing tumor immediately engendered a great deal of interest in this previously drab lesion and resulted in a great deal of experimental interest (116).

Soon after the clinical symptoms of carcinoidosis were described by Thorson and co-workers (165) it became apparent that increased intestinal motility, intestinal cramps, and borborygmi were characteristic of the metastatic stage of this syndrome, and a good deal of attention has been directed toward evaluating the effect of serotonin on gastrointestinal activity.

Serotonin is produced in argentaffin cells which are primarily located in the mucosal layer of the duodenum and the pyloric region (166) of the stomach. In the rabbit, serotonin is also found in the gastric corpus (56). Although it was originally thought that the malignant carcinoid syndrome resulted from carcinoids of the gastrointestinal tract only, a report by Warner and Soultren (172) indicates that the classic malignant carcinoid syndrome may occur in patients with malignant bronchial adenomas of the carcinoid type; they report 2 such cases and cite 2 other patients who probably exhibited this phenomenon.

Parenterally administered serotonin causes spasm of the smooth muscle of the intestine (53), and in man causes borborygmi and abdominal cramps (154). This vasoconstrictor substance diminishes acid secretion by the stomach (17) and causes an outpouring of alkaline mucus (153). The extent of serotonin release from the intestine is in part controlled by the nature of the diet, with meat and serotonin precursors such as tryptophan stimulating serotonin production (155). These actions of serotonin apparently are antiulcerogenic in nature, and carcinoidosis has not been associated with peptic ulceration.

More recent investigations of the gastroenterologic effects of serotonin suggests its possible role in altering or mediating the effects of several other drugs. Thus, it has been noted that serotonin partly blocks the gastric stimulatory effect of histamine, a property that in itself is inhibited by fasting (18) or atropinization (125). Reserpine causes a release of serotonin from the intestine (151), and a part of the gastric inhibitory effect of this drug is thought by Brodie to be due to serotonin (22). Still more recently it has been shown that chlorpromazine blocks the site of serotonin activity (14), and chlorpromazine has been said to be of value in diminishing the intestinal cramps associated with carcinoidosis (30).

Obviously, much remains to be discovered of the many facets of

serotonin activity, a number of which have interesting implications in their relation to gastrointestinal activity. The facts now available certainly indicate that serotonin is not ulcerogenic from a secretory standpoint. The lack of association of peptic ulceration with the malignant carcinoid syndrome clinically confirms this concept. The excessive gastrointestinal motility caused by serotonin apparently does not predispose to the development of peptic ulcer.

COMMENT

It is quite obvious from this review that there is no clear-cut relation between peptic ulceration and diseases of the endocrine glands in man. Although certain endocrine abnormalities such as hyperparathyroidism may often be associated with peptic ulceration, the mechanisms responsible for the frequent coexistence of these conditions are completely obscure. The many conflicting bits of evidence make the proper evaluation of the role of the endocrine glands in the pathogenesis of peptic ulceration extremely difficult. Investigations of the peptic ulceration occurring in hyperparathyroidism or during the administration of adrenocortical steroids would appear to be the most fruitful avenues for further study of this problem. Critical study of patients with the Zollinger-Ellison syndrome and those with adenomatosis is necessary to delineate clearly the responsible ulcerogenic factors in these cases. Great strides have been made in clarifying our knowledge of the gastrointestinal hormones which control gastric secretion. These advances will no doubt make our understanding of gastric physiology and therefore our approach to the clinical problem of peptic ulceration more intelligent and fruitful.

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Disorders Related to Disturbed Absorption of the Small Bowel*

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THE SUCCESSFUL THERAPIES for the sprue syndromes in the past decade have renewed interest in the pathophysiology of the small intestine. Malabsorption of nutrients is related to abnormalities in the small bowel mucosa. Adequate biopsy specimens and detailed cytologic studies have been helpful in understanding the columnar cell function. The present discussion is oriented toward an evaluation of the columnar cell and the mechanisms that cause dysfunction. For clarification, the anatomy and physiology of absorption by the individual columnar cell are presented for correlation with the epithelial disorders of clinical significance.

ANATOMY OF ABSORPTION

The movement of substances from the environment to the inside of a single cell may be defined as absorption. The cell seemingly has a continuous peripheral membrane, and yet normally allows substances to enter and leave. Absorption by the mammalian small intestine is a more complex task than that required by single cell organisms. Intestinal absorption is usually characterized by the appearance of the absorbed substances in the animal's extracellular fluid. Less direct observations have also been used when necessary.

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microscopy has demonstrated that adjacent cells are interlocked by folds of their plasma membranes. There is a lateral space between these cells which, in the case of fat absorption, receives lipid particles after their exit from the cell (137, 184) (Fig. 1). This pathway illustrates the complexity of structure and function inside the cell. Many intracellular compartments or organelles are present, such as the endoplasmic reticulum, Golgi apparatus, mitochondria, and nucleus of each cell. Each organelle consists of finer structures: membranes, particles, and matrices.

During intestinal absorption, substances may: *(1)* cross the continuous membrane of the microvilli, *(2)* traverse some distance within the complexity of the cytoplasm, and *(3)* exit from the cell across the plasma membrane. The absorbed substances then must cross the epithelial basement membrane, the extracellular space of the lamina propria, and, finally, the basement membrane and endothelial cells of the capillaries and lacteals. These vessels within each villus pick up substances by an unknown selective mechanism for distribution to the rest of the body. At present, there is no exact analysis of the function of any of these anatomic sites in the absorptive process.

PHYSIOLOGY OF ABSORPTION

The physiologic processes involved in intestinal absorption are obscure. There is at present inadequate information identifying those products of digestion absorbed selectively by the epithelium. Absorption may be an active process requiring the performance of work to transport substances from the single cell's environment to its cytoplasm. In the case of the small intestine, the columnar epithelium possesses active transport mechanisms (187). The increased concentrations of intracellular enzymes which the columnar cells acquire as they emerge from the crypts of Lieberkühn onto the sides of the villi attest to the nature of their active role (130, 172). Certain segments of the small intestine specialize in the absorption of specific substances; this is not related to surface area. Perhaps certain groups of cells can absorb some substances better than other, apparently identical cells.

"Active absorption" is the performance of electrochemical work (151). The transport of substances against an electrochemical gradient *is the evidence of such work. The ability of the small intestine to move* substances such as glucose from a lower luminal concentration to a higher blood concentration (against a concentration gradient) is an example (12). One aspect of "active" absorption by the intestine is the ability of the mucosa to prevent "leakage." Thus, the rate of entry into

The small intestine of man has the specialized function of absorbing the great bulk of his ingested food into the body fluids. This organ possesses an estimated internal surface area of 4 to 5 square meters (127). The intestinal lumen, in which many complex digestive events occur, is bordered by a mucous membrane, the folds and surfaces of which

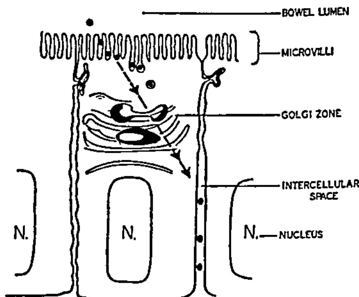


FIG. 1.—Schematic drawing of fat absorption through normal columnar cells. Fat droplets 300 to 500 Å in diameter *(black dots)* are present in lumen and between microvilli; below microvilli, a single fat droplet enclosed by membrane of the endoplasmic reticulum. The role of the Golgi zone is not well understood. Eventually, fat particles enter intercellular space and, finally, the lacteals. (Modified from Weiss (184) and Palay and Karlin (137a).)

contain enormous numbers of villi (see Plate I, *A*). Each villus is covered by many highly-differentiated epithelial cells derived from undifferentiated cells in the crypts of Lieberkühn (130, 172). The villous epithelium, containing high concentrations of intracellular enzymes, is capable of absorptive work. Numerous microvilli project from the luminal surfaces of the epithelial cells (193). Their functional role has not been fully clarified. The microvilli are constituents of the columnar cell's striate border. They are covered by a membrane about 105 Å thick, consisting of 2 opaque components, each about 40 Å thick, between which is a clear zone about 25 Å wide. There are no pores or holes in the membrane; it is continuous with the remainder of the cell's plasma membrane. The microvilli may increase the columnar cell's free surface area approximately 14 times (193). Electron

gests that it differs from dietary carbohydrates, which are absorbed completely in the upper 100 cm. of human small intestine (34). The intestinal absorption of D-xylose in man may occur by "diffusion" rather than by an active process.

FAT ABSORPTION.—Clinical observations have revealed an increased amount of fatty acids and triglyceride in the stools of many patients with sprue. It has been the impression that this increased fecal fat is derived from dietary fat because of impaired intestinal absorption (54a). The increased fecal excretion of I^{131}-labeled triolein by sprue patients supports this view. However, some patients with sprue lose more fat in their stool than had been present in their diets (58, 182), suggesting that phenomena in addition to absorption are measured by the intake-excretion (fat balance) type of study. The intestinal absorption of I^{131}-triolein is not equal to the intestinal absorption of fat (177). Factors other than triglyceride absorption are possibly measured by this procedure. The *rate* of fat absorption is not measured by either the fat balance or the fecal excretion of I^{131}-triolein. Clinical tests which measure the rate of entry of lipids into the blood indicate that there is impaired absorption of fat in steatorrheal states. However, the final proof of an impaired fat absorption may depend on evidence such as that obtained by the use of an intubation device (24), which permits sampling of the small intestinal contents after a standard meal containing a nonabsorbable reference substance.

Individual fats and fatty acids have different physical and chemical properties which influence their absorbability. Among these are chain length, degree of unsaturation, and liquidity at body temperature. The absorption of a lipid may be influenced by the fat in which it is dissolved (64).

The experimental animal displays a complicated series of motor and secretory events in the upper digestive tract in response to a fat meal. The fatty food mixture is gradually released from the stomach into the upper small intestine where it appears as an emulsified, bile-stained liquid containing hydrolyzed fat. Slightly later, the finely divided fat or its sudanophilic appearance may be grossly observed pouring through the intestinal lymphatic vessels into the thoracic duct from which it enters the blood stream. If the blood is sampled after a fat meal, the plasma is turbid because of many minute particles of fat (chylomicrons).

The entrance of fat into and across the intestinal columnar epithelium has been studied by electron microscopy, a method which has provided direct observations of digested fat entering and leaving the intestinal mucosa. After ingestion of whipped cream by adult mice,

the mucosa is higher than the rate of leakage into the lumen (188). No single hypothesis concerning mechanism explains the absorption of the numerous substances transported across the small intestinal mucosa. In general, the absorption of water and electrolytes, small organic molecules such as sugars, and large organic molecules such as proteins, may be caused by different mechanisms. Amebas can take up parts of their fluid environment by pinocytosis (106). The small intestines of suckling rats and mice may take up proteins and colloidal materials by a process similar to pinocytosis (51). Fine particles of insoluble azo dye are absorbed by intestinal columnar cells of adult rats (16). Electron micrographs have indicated that the products of fat digestion are absorbed in particulate form (137, 184). The full significance of these observations awaits evaluation.

Absorption of nutrients is necessary for all body cells. Products which are absorbed by the small intestinal mucosa are transferred in turn to the extracellular fluid. The nature of this activity is not clear, nor is it readily distinguished from the "absorptive phase." However, in the absorption of certain substances (cholesterol [33], vitamin B_{12} [28]), a considerable time elapses between these two phases. Although the extent to which defective transport may cause disease in various body organs may be obscure, it is a major physiologic abnormality in the sprue syndrome. Defective small intestinal absorption of nearly all foods occurs in sprue. This defect may result from a loss of cellular ability to transport substances as well as from a decrease in the amount of functioning tissue.

Absorption of Specific Substances

The particular substances to be discussed have been chosen because their intestinal absorption is of historic and clinical importance in relation to intestinal malabsorption. Thus, the gross appearance of steatorrheal stools has indicated the presence of impaired fat absorption. At the present time, the absorption of fat, vitamin B_{12}, and D-xylose (and glucose) are frequently employed parameters of small intestinal function.

The rate of glucose absorption is greatest in the upper small intestine. Glucose is absorbed against a concentration gradient (69). A recent extensive study has disclosed properties of sugars which are necessary for active transport (190, 191). The cellular mechanism for uptake of sugars having these properties is not known. D-Xylose is not transported actively by hamster intestine *in vitro* (191). It is found in human ileostomy drainage fluid after a 25 Gm. dose (18); this sug-

acids, mono-, di-, and triglycerides may be nearly in equilibrium during digestion within the intestinal lumen. It has been calculated that in man 35 to 40 per cent of triglyceride is hydrolyzed completely before absorption, while the remaining 60 to 65 per cent is partially hydrolyzed to a mixture of tri-, di-, and monoglycerides (32).

Glycerides and fatty acids are absorbed by the intestine. Long-chain fatty acids appear in the intestinal lymph, in contrast to the short-chain fatty acids which enter the portal blood (26). When labeled long-chain fatty acids were fed to rats, they were apparently absorbed as such and subsequently synthesized into triglyceride by the mucosal cells (29). A like process may occur in man (25). The blood glucose may be a precursor of the glycerol needed for this process (78). This newly formed triglyceride enters the intestinal lymph.

The percentage of glycerides absorbed from the digestive mixture has been identified by feeding rats triglycerides, the glycerol component of which was radioactive (144). About 55 to 75 per cent of this glycerol appeared in the intestinal lymph during absorption. This percentage is equivalent to the amount of glyceride absorbed. The remainder of the radioactive glycerol was equivalent to the amount of completely hydrolyzed glyceride. Free glycerol which was absorbed from the lumen was not re-utilized for triglyceride synthesis by the intestinal mucosa. A similar percentage of glycerides may be absorbed from the triglyceride digestive mixture in man (32). Glycerides and free fatty acids may be absorbed almost simultaneously as a mixture from the intestinal chyme. Borgström (32) has suggested that digested triglyceride is absorbed in the form of micelles. This hypothesis might lend support to the particulate absorption of fat which has been observed by electron microscopy.

Analysis of the intestinal wall of rats at various times after feeding fats has revealed the accumulation of glyceride, and possibly fatty acid during the absorptive process (29). Study of the intestinal wall has given some indication of the site of absorption. Gage and Fish (79) noted that fat absorption occurs mainly in the middle portion of the small intestine of cats, as judged by the presence of absorbed Sudan III in the mucosa and lacteals. The more distal small intestine was regarded as the main site of absorption of I^{131}-triolein in rats (17). The middle of the small intestine of dogs was considered to be the main site for absorption of this radioactive compound (175). In man, the duodenum and upper jejunum absorb most orally administered fat as determined by sampling of luminal contents (34). Exposure of the mucosa of both upper and lower intestinal segments of hamsters *in vitro* to the same concentration of fatty acids showed that they are

electron micrographs of the duodenal epithelium revealed lipid bodies located in large Golgi vacuoles and in the apical cytoplasm surrounded by smooth membranes. Three hours after feeding, the lipid bodies (fat droplets) were present in the spaces between columnar cells, in the extracellular connective tissue space of the lamina propria, and inside the central lacteals of the villus (184). Fat droplets were not observed in the striate border. It was postulated that extremely minute fat particles (less than 40 Å) had entered through the striate border and increased in size to become the lipid droplets observed in the electron micrographs. The Golgi complex transported lipid droplets to the spaces between the columnar absorptive cells. However, this study infers that the digestive products of whipped cream could not be observed as they were entering the epithelium and were perhaps of molecular size. The droplets emerging into the minute lymph vessels may represent the early postabsorptive chylomicrons.

In the jejunal epithelium of rats fed corn oil, electron-dense droplets (300 to 500 Å) were visible between microvilli and in the subadjacent cytoplasm (137). This observation of lipid droplets on both sides of the striate border suggested that fat is absorbed in particulate form.

More recently, Palay and Karlin have presented the further intracellular pathway of fat absorption. The minute droplets which were formed from the digestion of corn oil were observed to enter the absorptive cells from the lumen by means of pinocytosis. The lipid droplets appeared to travel within the canalicular network of the lateral intercellular space. The endoplasmic reticulum was regarded as being more important than the Golgi complex in the intracellular transport of lipid (137a).

Investigations of the *final* chemical form in which the products of fat digestion are presented to the intestinal epithelium for absorption are crucial for an understanding of the nature of fat absorption. The experimental approach has included studies of the digestive mixture, the intestinal mucosa, and the lymphatic chyle during absorption. The absorption of compounds containing fatty acid chains of less than 16 carbon atoms will not be discussed.

Analysis of digestive mixtures performed *in vitro* and *in vivo* has revealed that the triglycerides of long-chain fatty acids are hydrolyzed to di- and monoglycerides and free fatty acids. The free fatty acids recombine with the mono- and diglycerides to form diglycerides and triglycerides respectively (4, 31). The over-all reaction proceeds in the direction of complete hydrolysis, since glycerol does not combine with free fatty acid under the influence of pancreatic lipase (30). Fatty

using everted sacs of rat intestine revealed that intestinal uptake of B_{12} required its presence simultaneously with I.F. (170). Preliminary incubation of the intestinal mucosa with I.F. alone, followed by washing, did not stimulate B_{12} uptake when the same intestine was subsequently incubated with only the B_{12}.

Experiments in man and rat have indicated that the binding of this vitamin to I.F. may prove to be vital for absorption (21, 134, 160). However, it is possible that this binding may represent the union of the vitamin with binding substances other than I.F. A chemically pure I.F. has not been definitely isolated. The ability of an I.F. preparation to bind B_{12} may decrease with progressive purification of intrinsic factor (116, 188), and it is therefore still questionable whether this binding occurs and is necessary for the absorption of B_{12}. As stated above regarding fat absorption, we are again confronted with the problem of the identity of materials in the lumen of the small intestine which are selectively absorbed by the mucosa. A possible theory suggests that a protein in the gastric juice binds B_{12}, and that intestinal absorption of this complex is stimulated by I.F. (114, 186). Another recent theory has stated that I.F. is initially bound to special receptors on intestinal absorptive cells in the presence of calcium ions. The adsorbed I.F. then binds B_{12} by a physical process. This theory was based on data showing that hog I.F. stimulated the uptake of B_{12} into the rat intestine *in vitro* (102). However, such an observation is in conflict with published reports indicating that hog I.F. does not stimulate B_{12} absorption in gastrectomized rats (50, 52, 135, 174, 181), and in fact may inhibit absorption in unoperated rats (53, 152).

Nevertheless, an interaction among I.F., B_{12}, and the intestinal mucosa is necessary, although the mechanism by which the vitamin is selectively absorbed remains unknown. There are species differences in both the small intestine and I.F. preparations as regards the absorption of B_{12}. This may indicate a highly specific role for the intestinal mucosa and I.F. in this mechanism (171). The vital role of the intestinal mucosa is intimated by observations that specific segments of small intestine are responsible for B_{12} absorption. The location of these segments varies in different species (10, 27, 28, 115, 147, 171). *In vitro* experiments have shown confinement of B_{12} absorption to segments to be obligatory and not dependent on the mechanics of intraluminal transit (171). In the case of man, B_{12} absorption occurs in the ileum (27). Localization of radioactive B_{12} with a scintillation probe during laparotomy demonstrated increased radioactivity in the ileum (Fig. 2). Patients with ileitis (122) or resection of the distal small bowel (59) had impaired radioactive B_{12} absorption and fre-

absorbed most rapidly in segments of the upper small intestine (108). Fatty acid absorption is inhibited under anaerobic conditions, implying an "active process" (107).

VITAMIN B_{12}.—The absorption of vitamin B_{12} by the small intestine has presented an extraordinary phenomenon for research since it requires the presence of a substance produced in the stomach, the intrinsic factor (I.F.) of Castle. Initially, investigation of the role of I.F. in the absorption of B_{12} was limited to the study of patients with pernicious anemia who lacked the ability to manufacture adequate I.F. B_{12} absorption could only be measured in pernicious anemia patients in relapse, as indicated by their enhanced hematopoietic response. The preparation of the radioactive vitamin has permitted more direct methods for observing the stimulation of its intestinal absorption by I.F. An intrinsic factor mechanism for the intestinal absorption of B_{12} in the experimental animal was discovered with the aid of isotopic technics. Gastrectomized rats required an orally administered I.F. preparation derived from rat stomach for the intestinal absorption of physiologic amounts of B_{12} (52, 135, 174, 181). More recently, *in vitro* methods have been used to study the intestinal absorption of radioactive B_{12} (101, 170).

Vitamin B_{12} is a cobalt-containing compound of known chemical structure. The gastrointestinal mucosa is nearly impermeable to physiologic concentrations of B_{12} within the lumen in the absence of I.F. Intrinsic factor has not been definitely isolated, but preparations of varying properties have been described (105, 116, 188). Most of the purified intrinsic factor preparations have been obtained from hog stomach. However, the identity of intrinsic factor may vary in different species, as first suggested by experiments using B_{12}-deficient rats fed the vitamin with a hog I.F. preparation. Their growth was impaired in comparison to rats fed only B_{12} (53). The absorption of radioactive B_{12} fed to B_{12}-deficient and normal rats was impaired by hog I.F. (152).

The mechanism by which physiologic amounts of B_{12} are absorbed is not known, and the solution of this problem is tightly linked with the role of intrinsic factor. A theory to explain this phenomenon must be compatible with data accumulated on the interreactions of B_{12} and I.F. Is it necessary for B_{12} and I.F. to combine before absorption? In 1953, data from pernicious anemia patients had suggested that B_{12} was absorbed if fed 4 hours after orally administered I.F. (180). In 1957, it was shown that the radioactive vitamin was inadequately absorbed when it was administered 30 minutes or more after I.F. (rat gastric juice) in gastrectomized rats (134). More recently, an *in vitro* method

No persistent or "resident" flora were located in the jejunum or upper ileum either by sterile intraluminal aspirations through various type of oral suction or by needle aspiration of the bowel lumen during laparotomy procedures (5, 61). The few coccal types present are considered contaminants from the oral cavity. The presence of gastric acidity is a major factor in the inhibition of bacterial growth in the proximal small bowel (13). Efforts to find an abnormal bacterial flora in the small bowel in tropical sprue and celiac disease have not been successful (6, 132).

Malabsorption of foodstuffs in the small bowel may allow an overgrowth of bacteria in the colon, which in turn permits a cephalad spread of the flora into the ileum. Indeed, in cirrhosis the increased concentration of "resident" bacteria in the ileum (126) is probably related to the mild steatorrhea found in hepatic dysfunction (96).

ANATOMIC ALTERATIONS

GASTROCOLIC FISTULA.—The steatorrhea and negative nitrogen balance in this disorder are, for the most part, not associated with a short-circuit diversion of food directly into the transverse colon. The bulk of an oral barium meal enters the small bowel. In fact, the fistula between the stomach and colon may best be demonstrated by inflow of barium from the colon into the stomach (142). Often, the small bowel pattern exhibits clumping and segmentation similar to the irregularities noted in idiopathic steatorrhea. Dogs with artificial fistulas have a similar pattern, suggesting that the weight loss and diarrhea are associated with malabsorption rather than a short circuit from the stomach to the colon (146). Microscopic examination of the jejunum reveals edema of the villi and cellular infiltration of the lamina propria, supporting a concept of jejunitis, an irritative change of the small bowel caused by the profusion of bacteria entering the stomach from the colon. Bacterial metabolites, such as fatty acids and lactic acid, may be agents altering the small bowel x-ray pattern (73). This concept has clinical support from the excellent responses obtained by cecostomy, in which patients showed nutritional improvement after the diversion of the ileal stream and depression of bacterial growth in the transverse colon which could contaminate the stomach pouch (141). This anatomic disorder is the outstanding example of bacteria in the proximal small bowel with induction of jejunitis and malabsorption by a profuse colonic flora.

DIVERTICULA.—Recent clinical reports have emphasized that jejunal diverticula are associated with macrocytic anemia and steatorrhea (9,

quently B_{12} deficiency, as determined by bioassay of their serum (128). Tests of B_{12} absorption might indicate the functional status of the distal small bowel in man (27). Patients with sprue are apt to have impaired B_{12} absorption.

In vivo, increasingly large doses of orally administered B_{12} beyond

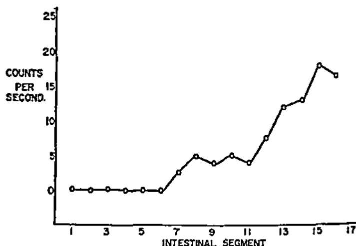


FIG. 2.—Localization of radioactive vitamin B_{12} in segments of human small bowel measured during laparotomy 3 hours after oral ingestion of vitamin B_{12} plus I F. Segment 1 is adjacent to ligament of Treitz, segment 17 is near ileocecal valve; increased radioactivity in segments 11 through 17 indicates that most of the vitamin B_{12} absorption occurs in ileum. (Modified from Booth and Mollin (27))

a certain limit result in a diminishing percentage of absorption (92). This nonlinearity implies the saturation of some absorptive mechanism. Finally, there is an apparent delay of 1 to 2 hours before absorbed B_{12} leaves the intestinal wall to enter the remainder of the body (27).

EFFECTS OF BACTERIA ON ABSORPTION

Normal Bowel

There is no evidence that the normal bacterial flora participate in the absorption of foodstuffs in the small bowel. With free gastric acidity, the small bowel in the fasting state is a moist, collapsed, relatively sterile mucosal tube. Usually, it is difficult to aspirate mucus from the duodenum, jejunum, or upper ileum from subject in a fasting state. While there is some continuous secretion, the volume is small, and most efforts have been associated with intraluminal irritation to promote secretion (82).

Enlarged cul-de-sacs prepared by surgical change of the small bowel in rats must have the chyme flow into the pouch to cause dilatation (stagnation) before macrocytic anemias and impaired absorption of labeled vitamin B_{12} can develop (47).

Intestinal absorption of B_{12} in man primarily occurs in the ileum (27). Any functional changes of this limited area for absorption may cause depletion of body stores of B_{12}. Strictures in the proximal colon or ileum with profuse bacterial flora impair absorption; the exact mechanism is not known (98, 99). If it is associated with a mild inflammatory response from the bacteria, or by-products of their metabolism, treatment with antibiotics (except neomycin) will correct the B_{12} malabsorption and restore normal serum levels. Girdwood (91) reported that the predominant organism found in bacterial cultures of blind loops during surgical repair in 5 patients was Escherichia coli (91). *In vitro* studies demonstrated active utilization (uptake) of labeled B_{12} by the organism. The bacteria did not require folic acid, pantothenic acid, methionine, or phenylalanine (90). This is the first laboratory evidence to suggest that bacteria could deprive the patient of B_{12} but not of folic acid. There is no information to assess possible *in vivo* bacterial binding or utilization of B_{12} and/or I.F. Anatomic alterations in the ileum are not connected with impaired absorption of folic acid (60).

These recent observations help to understand the evolution of B_{12} depletion in pernicious anemia. The absorption defect related to intrinsic factor is not an absolute but rather a relative inadequacy. Pooling gastric juice aspirations from several patients with pernicious anemia will allow a hematologic response in an untreated patient with severe macrocytic anemia (93). The absence of gastric acidity contributes to a cephalad extension of the colon flora into the more proximal areas of the small bowel (94). Prolonged administration (15 to 20 days) of chlortetracycline to pernicious anemia patients in relapse has initiated a reticulocyte response and erythropoiesis (121). Although the hematologic response was slow, it was evident that the small amounts of I.F. available were adequate to promote partial absorption of dietary B_{12}. This may be attributed to a decreased bacterial flora in the ileum available to compete for the limited intrinsic factor and/or B_{12}. Before the advent of liver extract therapy, untreated patients benefited from ileostomies which protected the ileum from the colon bacterial flora (65, 162). As the ileostomy secretions were "sterilized," these patients experienced a partial hematologic remission. Such heroic surgery performed a useful physiologic experiment similar to the diversion of bacterial flora after cecostomy in gastrocolic fistula.

87). Diverticula of the small bowel are common in many elderly patients, but are rarely correlated with such complications (119). The diverticula affecting absorption are of moderate size and are located in the jejunum. Duodenal diverticula probably are kept sterile by the acidity of the gastric secretion. Roentgenographic study of patients with malabsorption and diverticula has revealed large saccular dilatations but bacterial samplings of these sacs have not been reported. While intubation studies to obtain cultures have not been performed, the diverticula probably allow bacterial growth from entrapped food particles and secretions from the propulsive luminal stream. With the bacterial overgrowth, bacterial spillage into the distal bowel fluid flow may be expected, with an irritative mucosal reaction, just as with gastrocolic fistula. Since certain strains of Streptococcus faecalis produce fats (41, 158), the bacterial flora could contribute to a chemical irritation by fatty acid formation from such fats in the presence of normal pancreatic enzymes (82). Ingestion of fatty acids with a barium meal in normal subjects will simulate the roentgenographic "deficiency" pattern of the small bowel, as in sprue patients. Absorption of B_{12} labeled with radioactive cobalt is impaired in these cases. While the bacterial flora may combine with this vitamin, Badenoch *et al.* (9) could demonstrate some improvement in B_{12} absorption with increasing amounts of purified I.F. (in excess of those which enhance B_{12} absorption in pernicious anemia). No information is available to explain the mechanism by which excessive I.F. enhances B_{12} absorption.

Oral administration of tetracycline derivatives improves absorption of labeled B_{12} and lessens steatorrhea. Such evidence is the only supporting data to suggest an abnormal bacterial flora. No study by biopsy is available to define changes in the bowel mucosa, if they exist.

"BLIND LOOPS" AND STRICTURES.—Alteration of the bowel circuit between the ileum and transverse colon in regional ileitis is the most common mechanism for "blind loops" (82). As with small bowel diverticula, most patients with anastomoses do not manifest nutritional changes. The collection of luminal nutrients and secretions in a bowel area with sluggish flow is an important factor in maintaining an abnormal bacterial growth. An anastomosis of ileum to the transverse colon which allows the liquid ileal contents to be propelled toward the cecum is more likely to initiate a stagnant pool of digested nutrients (14). A side-to-side union which allows some of the ileal contents to progress toward the ileocecal valve would be a potential nutritional pool for bacterial growth. Most of these "blind loops" or enlarged cul-de-sacs have been associated with megaloblastic anemias and have been associated with only mild steatorrhea and weight loss (46, 66).

controlling the diarrhea associated with fulminating kwashiorkor. The decreased concentration of plasma proteins may impair bacteriocidal functions of the bowel secretions, thus allowing the sudden onset of diarrhea from an explosive growth of the bowel flora in this disorder (167).

HYPOGAMMAGLOBULINEMIA

Recent clinical studies have demonstrated a high incidence of steatorrhea and diarrhea in the adult type of acquired hypogammaglobulinemia (159, 192, 194). While the main emphasis has been on evaluation of repeated infections, elevated fecal fat excretion and abnormal small bowel x-ray patterns of the barium meal have been observed in some patients. Some improvement has been obtained with oral antibacterial agents, but the diarrhea has been controlled more completely with frequent injections of gamma globulin (194). There is no explanation for this response. If the injections of gamma globulin are not given frequently, the diarrhea (? steatorrhea) recurs; this has led to the speculation that the succus entericus may have bacteriocidal effects if adequate antibodies are available. While there are no observations to suggest abnormal function of the columnar cells in the intestinal mucosa, marked hypertrophy of the lymphatic nodules in the lamina propria has been noted (68). Observations are not yet adequate to explain whether this hypertrophy represents an effort to supply bacteriocidal function for the succus entericus.

SPRUE SYNDROME

CLINICAL OBSERVATIONS

Sprue is a clinical syndrome characterized by diarrhea and weight loss, and associated with impaired absorption of foods, minerals, and water by the small bowel (83). The mechanisms initiating malabsorption are diverse, but the final result impairing transfer of food substances across the mucosa is similar. The body economy is depleted of nutritional reserves of fats, proteins, and vitamins at varying rates, depending on the intake of these materials and the degree of partial absorption. There is a wide spectrum of clinical syndromes related to the duration of impaired absorption.

Much confusion has been linked with efforts to compare various types of malabsorption. Comparison of clinical observations should be correlated with the duration of the disorder and the patient's nutritional status. The disorders described by clinicians in tropical areas

Antibiotic Therapy

Some patients with tropical sprue have responded to antibiotic and sulfonamide therapy (41, 76). Efforts to establish the presence of an abnormal bacterial flora in the small bowel have not been successful (132). Nevertheless, these patients have gained weight and steatorrhea has improved during and after treatment. Is it possible that antibiotics improve nutrition and absorption in the sprue patient by decreasing the bacterial population and "sparing" nutrients for the host? Numerous animal studies have indicated that antibiotics will allow growth even with suboptimal nutrition (111). Since the tropical sprue patient may have adequate body stores of folic acid (45), can a hypothesis be constructed to explain impaired utilization of this vitamin? The metabolism of the aromatic amino acids may be a signpost of the bacterial function. In the presence of ascorbic acid deficiency (scurvy), increased urinary excretion of the hydroxyphenylic acid derivatives of tyrosine and phenylalanine is sometimes found (131, 150). With ascorbic acid therapy, these abnormal metabolites disappear. Boscott and Cooke (35) noted that nontropical sprue patients had increased urinary concentrations of *p*-hydroxyphenylacetic and *p*-hydroxyphenylactic acids which disappeared when patients were "saturated" with ascorbic acid. No attempt was made to alter the bacterial flora. Excess ascorbic acid may have corrected a tissue malutilization of these aromatic amino acids, or allowed a more complete degradation of these metabolites by the bowel bacteria with adequate ascorbic acid to support tyrosinase activity. In the patients studied by Boscott and Cooke, vitamin C administration led to increased hemoglobin values and decreased macrocytosis of the red blood cells. In this instance, the excess ascorbic acid may have been of importance for the conversion of folic acid to the biologically active folinic acid for erythropoiesis (136). Evaluation of folic acid metabolism after administration of large doses of ascorbic acid would be helpful in clarifying this hypothesis in tropical sprue. Recent observations of adequate tissue levels of folic acid in the plasma buffy coat indicate that the disorder can no longer be related to a specific nutritional deficiency, but rather to mechanisms that impair the utilization of folic acid in cellular metabolism (45).

Additional support for the concept that antibiotics may decrease nutritional competition by bacteria is demonstrated by improvement of megaloblastic anemias in African natives treated with penicillin. In these patients, an abnormal bacterial flora supported by a bulky high carbohydrate diet has been assumed to alter utilization of hematopoietic substances (70). Antibiotic therapy has also been of value in

represent early changes in small bowel function; indeed, some patients may have symptoms for days or weeks before the diagnosis is made. These patients may not manifest marked nutritional deficiencies, since they have not been ill long enough to deplete body stores. For simplification, this type of patient has been classified as being in Stage I of the disorder (84). With more prolonged illness, the progressive malabsorption produces the clinical signs of vitamin deficiency, iron deficiency and weight loss (Stage II). For the most part, these are early manifestations seen only in tropical sprue; possibly, patients with childhood celiac disease could be included in this stage. In many instances, the adult patients studied in the temperate zone have had malabsorption for years before the diagnosis has been made. The altered functions of bowel and bone marrow and the depletion of tissue nutrients have had many years to influence the bowel mucosa adversely (Stage III). Often, these changes may be lessened by the patient's use of vitamin supplements. Similarly, there are patients in tropical areas with intermittent malabsorption of long duration (85). The adult patient with idiopathic steatorrhea or nontropical sprue has had a long-standing chronic disorder of bowel function and should not necessarily be compared with the tropical sprue patient who may have a brief history and possibly a self-limited disorder.

The passage of unabsorbed fats and carbohydrates into the colon allows excessive fermentation to produce the bulky, watery, foul-smelling stools so characteristic of sprue syndromes. Frequency of bowel movements is not as important diagnostically as the bulk (volume) of stool excreted. The concomitant loss of electrolytes with the stool is an important cause of weakness and lassitude (22, 123). Prolonged malabsorption may be manifested by the clinical signs of vitamin deficiencies, i.e., glossitis, pigmentation, follicular skin changes, and anemia. Contrary to the emphasis placed in the past, the hematologic disorders of the sprue syndromes represent a nutritional deficiency rather than a basic etiology of the illness (57).

Laboratory observations.—The sprue syndromes are associated with impaired absorption of simple molecular materials such as water, urea, sodium chloride, potassium iodides, calcium, and iron salts (84). With changes in transfer of simple structures across the mucosa, it is quite understandable that absorption of the more complex end products of digestion is impaired. The substances tested have been limited to items for which laboratory technics are available, i.e., fats, cholesterol, phospholipids, vitamin A, vitamin C, vitamin B_{12}, folic acid, carotene, alpha-tocopherol, glycine, proline, urea, glucose, fructose, and D-xylose. By inference, low fasting levels of serum constituents

Clinical Phases of Idiopathic Sprue

Classification	Duration	Hematologic Features	Bowel Malabsorption	X-Ray Pattern of Small Bowel	Signs and Symptoms
Stage I (early phase) (Tropical sprue)	Weeks to months	Normal	None to mild	Early changes	Mild
Stage II (deficiency phase) (Tropical sprue; ? early celiac disease)	Months	Hypochromia and/or macrocytosis	Moderate to severe	Abnormal	Secondary deficiencies
Stage III (macrocytic anemia) (Tropical sprue; nontropical sprue [adult celiac disease])	Months to years	Hypochromia and/or macrocytosis	Severe	Abnormal	Multiple deficiencies

DIAGNOSTIC MEASUREMENTS

With the numerous procedures available for diagnostic study, what can the clinician use to determine the presence of malabsorption? We have found the following procedures helpful, but they do not necessarily represent the final solution in clinical practice.

BLOOD CONSTITUENTS.—The plasma or serum levels of nutrients may indirectly reflect body stores. The fasting serum carotene is the most valuable guide available to indicate impairment of fat absorption (2, 185). The serum iron and cholesterol measurement may be useful corollaries.

ORAL TOLERANCE TESTS. *Urinary excretion of d-xylose.*—The value of this test has adequate clinical documentation (18, 67, 176). Normal subjects excrete 4.5 to 7.0 Gm. 5 hours after an oral dose of 25 Gm. of this pentose, and absorption is not impaired by pancreatic disorders (36). The sprue patient may excrete from 0.2 to 4.0 Gm., and values below 3.0 Gm. in 5 hours should lead to a search for other parameters of malabsorption.

Fat absorption-lipemia curve.—For convenience, the lipemia response to a test meal containing butter fat or olive oil has been employed. Evaluation of serum turbidity as an index of lipemia at 5 hour intervals has been as reliable as any specific chemical measurement of fat. While various units have been used to define lipemia, a simple curve of absorption may be obtained by measuring the optic density (O.D.) of the serum in any colorimeter at 650 A. Normal subjects will have an O.D. greater than 0.1 by the third or fourth hour after ingestion of 30 Gm. of butter fat (80).

Vitamin A.—Serum levels following ingestion of 300,000 units of vitamin A at 5 and 7 hours have been a satisfactory assay of fat absorption. The serum levels should rise above 75 μg. per 100 cc. by the fifth hour and 125 μg. at the seventh hour (120).

X-RAY PATTERN OF SMALL BOWEL.—Roentgenography is essential to exclude anatomic alterations of the bowel (blind loops, strictures and fistulas, and diverticula), as well as to demonstrate a "deficiency pattern" (74, 124).

BIOPSY.—The clinical findings of secondary invasive disease of the submucosa cannot be separated from the idiopathic types of sprue with apparent epithelial defects. The availability of intraluminal biopsy instruments now allows a histologic diagnosis, and efforts should be made in all instances to confirm the clinical and laboratory findings with microscopic study of the jejunal mucosa (62, 163, 164). Although these procedures are by necessity "blind," in most instances the bowel mucosa usually is involved, with cytologic changes throughout.

have been considered evidence of impaired absorption, and if the diet has been adequate, this assumption may be accepted. For convenience, effective absorption of test agents has been evaluated by rates of absorption in a specified time interval (oral tolerance tests). Such procedures usually "stress" the bowel for maximal absorption in a relatively short time. They are advantageous for simplicity of performance. The time-honored oral glucose tolerance test should be discarded, for the intervals of sampling yield "flat curves" suggesting impaired absorption in about 40 per cent of adults (80).

In the patient with mucosal malabsorption, the x-ray pattern of the small bowel is changed after ingestion of an oral barium meal suspension. Films of the bowel area taken at 1 and 2 hour intervals will reveal a "deficiency pattern" of segmentation and flocculation of the barium with dilatation of the small bowel loops (3, 124). These roentgenographic alterations have been attributed to changed mucous secretion in the bowel lumen. *In vitro* mixtures of mucus and barium have demonstrated changing of the barium suspension as the concentration of mucus is increased (73).

BOWEL SECRETIONS.—There is little information at hand regarding the bowel secretions in malabsorption syndromes. A few observations have been made in tropical sprue. The soluble mucoproteins that can be measured in the aspirated succus entericus are decreased in the tropical sprue patient (86). This change may represent: (1) an altered secretion by the distorted epithelium; (2) a residual mucoprotein available from a more viscid mucoprotein adhering to the epithelium; or (3) an altered rate of absorption of soluble mucoproteins from enzymic secretions. Nasset and co-workers (133) have estimated that 50 to 100 Gm. of protein are excreted into the bowel lumen daily as digestive enzymes. Dysfunction of the epithelium may allow intestinal secretions to remain in the bowel lumen, where they may cause the viscid succus entericus reported in tropical sprue (166).

It is reasonable to expect that malabsorption would allow these proteins to descend into the distal bowel, thus enhancing utilization of foodstuffs by colonic bacteria. Evidence for excretion of protein into the bowel lumen also may be inferred from the fecal excretion of intravenously administered I^{131}-labeled polyvinylpyrrolidone (P.V.P.) with a molecular weight of 40,000 (95). In one study, a sprue patient excreted more I^{131}-P.V.P. than noted even in patients with hypercatabolic hypoproteinemia associated with hypertrophic gastritis (161). This material cannot be metabolized, so that the fecal excretion reflects the full capacity of the bowel to allow proteins (assuming that the transfer across the intestinal and gastric membranes is equivalent) to move into the bowel lumen.

serum complement-fixation antibodies to cereals containing gluten. Ingestion of gliadin will decrease the circulating level of such antibodies; this suggests "binding" of the antibody by the absorbed glutamine-peptide complex. Further evidence of this mechanism is necessary, for an immunologic reaction at the site of absorption may be a contributing factor to the cytologic changes (113).

At present, observations on therapy with antibiotics alone in a large group of nontropical sprue patients are lacking.

PATHOLOGY.—Research in the past 15 years has supplied clinical-pathologic correlations for the understanding of nontropical sprue. Abnormalities in the small intestine of patients with impaired absorption have been observed at autopsy (103) and at laparotomy (138). Frequently, the small intestine has been found to be dilated, a finding confirmed roentgenographically. The mucosa may be grossly "atrophic." Specimens obtained at autopsy and laparotomy sometimes display edema and cellular infiltration of the lamina propria of the mucosa and submucosa, and pigmentation of smooth muscle may also occur. Abnormalities of the intrinsic ganglia of the intestine have been described.

The introduction of intestinal aspiration biopsy tubes (62, 163) instigated a new phase of research which permitted cytologic correlations with clinical data. Since ultrastructural changes occur very rapidly after the columnar epithelium is deprived of oxygen (193), only tissue obtained by biopsy for fixation within minutes is of value for detailed cellular study. Occasionally, these tiny specimens may not be representative of the entire small intestinal mucosa, as was demonstrated by a remarkable case of patchy atrophy obtained at laparotomy (139); however, aspiration biopsy specimens for the most part do contain the diffuse changes observed at laparotomy (63).

In this connection, it may be of value to correlate aspiration biopsy specimens with x-ray studies of the small bowel, as well as with information obtained at autopsy and laparotomy. This may be particularly relevant in the use of the term "atrophy." Intestinal dilatation is characteristic of sprue, and it is reasonable to assume that it will result in a thinning of the intestinal wall, including the mucosa. Since this phenomenon has not been adequately described in many autopsy and laparotomy studies, it may be difficult to assess in aspiration biopsy studies. True atrophy may exist, but there is uncertainty about the meaning of this term and whether it designates the villi, the crypts, or the full thickness of the intestinal wall.

The following mucosal abnormalities have been observed: short, blunted villi, a thickened "crypt" layer, abnormal columnar cells,

One report of "patchy" distribution of the pathologic changes may suggest the need for repeated biopsies, especially if other laboratory evidence supports a diagnosis of bowel malabsorption (139).

Nontropical Sprue (Childhood and Adult Celiac Disease)

Etiology.—In contrast to tropical sprue, malabsorption syndromes in the temperate zones represent a more chronic disorder. Unfortunately, no information is available regarding changes in absorption shortly after onset. In all instances of adult sprue, the process may have been present for years, indeed decades, before a diagnosis was confirmed (57). In some instances, the patient has adjusted to the chronic malabsorption and has experienced transient remissions.

The discovery of gluten as an irritant or etiologic agent in childhood celiac disease has been applied to adult therapy. Although it is difficult to maintain rigid dietary supervision, most patients show improvement if gluten from wheat, rye, and barley is excluded from their diet (7, 8, 37, 77, 178). Much effort has been directed to elucidating the particular component of the gluten protein responsible for malabsorption. At the present time, gliadin appears to be the active principle (179). Its ingestion by the celiac patient results in increased blood levels of glutamine, even after a clinical remission on a gluten-free diet (183). Such an observation has suggested a cellular enzymic defect in the bowel mucosa regarding the metabolism of gliadin, since the normal subject does not show similar high blood levels of glutamine. Partly hydrolyzed gliadin will initiate steatorrhea if included in the diet, suggesting that a glutamine-containing peptide complex is the offending derivative (178). If this peptide fraction is incubated with fresh porcine small bowel mucosal extract, the complex becomes inactive when fed to celiac patients (72). This observation has supported the concept that the celiac patient has some intracellular enzymic defect for the metabolism of gliadin. Bowel dysfunction improves slowly if gluten is excluded from the diet (7). Probably, this delayed recovery is related to the prolonged period of malfunction with altered cytologic changes. French (77) has suggested that a patient should remain on a gluten-free diet for at least 200 days before any decision regarding therapy can be made. Both the high familial incidence of the disease (57) and the evidence for enzymic defects (72, 172, 183) suggest that the etiology of nontropical sprue is partly genetic.

Berger (19) has demonstrated that celiac patients may have special

villous epithelium. The chief cells on the villi are taller and have less rounded nuclei in comparison with crypt cells; their microvilli are well developed. Two distinct zones of normal epithelial cells have been observed: (*1*) an immature population in the crypts possessing mitotic activity but relatively slight capability for enzyme synthesis; and (*2*) older cells on the villi possessing unique histochemical and morphologic characteristics. These characteristics are undoubtedly related to the absorptive function of villous epithelium.

Mucosal changes in nontropical sprue represent a distortion of the normal patterns of growth and differentiation. There is, usually, a widened crypt layer with shortened blunted villi to indicate an increased number of epithelial cells which are not exposed to the absorptive surface. In fact, in many instances the villous projections are almost absent (Plate 1, *D*). The epithelial cells of the crypts tend to resemble the normal pattern. There is a zone of cellular maturation, characterized by cytoplasmic enzyme activity at the outlet of the crypts. However, the epithelium on the absorptive surface has decreased histochemical enzymic activity compared to the normal (172). We do not know if these alterations of villous cells at the bowel lumen cause lessened absorptive function, but such changes may represent the biochemical defect of malabsorption. In addition, electron microscopy has revealed diminished microvillous projections (100, 172) (Plate 2). The blunted villi may reduce the surface area to 20 per cent of normal (38). The microvilli may account for 95 per cent of the functional absorptive area of the small bowel (100). Abnormalities of the microvilli (brush border) may then reduce the potential area of active absorption to less than 20 per cent, depending on the degree of change present. In 2 cases of nontropical sprue, the pathologic appearance of the villi and microvilli reduced the absorptive area to 5 per cent of normal (100). The available surface area of digestant contact may be as important as any cytologic abnormality in the columnar cells as a mechanism for malabsorption.

The normal villus has an orderly palisade arrangement of the epithelium, with the nuclei of the columnar cells located in the proximal third of the cell (Plate 1, *C*). In contrast, the cellular arrangement is disorganized and the nuclei are altered in size and shape in nontropical sprue (Plate 1, *D*). The epithelial cells are flattened and cuboidal, with decreased cytoplasm. In contrast to tropical sprue, the mucosa of nontropical-sprue patients appears to have less inflammatory reaction, characterized by leukocyte infiltration among the columnar cells (43).

Increased mitoses of epithelial cells have been noted in nontropical

dilatation of the lumens of Lieberkühn's crypts and Brunner's glands, and cellular infiltration of the lamina propria (Plate I). Similar changes have been noted in childhood celiac disease (154, 156). Mucosal ulcerations have been seen at autopsy in the small bowel (104, 157). Ulcerations containing numerous long, rod-shaped bacilli were also found in 1 case that came to autopsy (112). The presence of similar bacilli in mesenteric lymph nodes in the same case was interpreted as evidence of bacterial invasion.

There are variety and inconstancy in many of the morphologic changes. A recent study of the intestinal mucosa of nontropical sprue patients and control subjects has attempted to demonstrate the pathogenesis of these changes (172).* All specimens were obtained by aspiration tube biopsy.

Consideration of the normal structure and function of jejunal epithelial cells is necessary to understand the changes in both nontropical and tropical sprue. As observed in laboratory animals, the normal chief and goblet cells originate in germinative areas of the crypts of Lieberkühn. These epithelial cells migrate onto the villous surface and eventually are sloughed from the villous tips into the bowel lumen (117). After migration from the crypts, the epithelial cells do not display mitotic activity. Similarly, aspiration biopsies of human jejunal mucosa (172) as well as specimens of human duodenum obtained at surgery (20) have revealed localization of mitoses in the crypts. Data obtained from human subjects are therefore also compatible with the theory of renewal of intestinal epithelial cells as proposed by Leblond and Stevens (118).

The villous epithelium consists of differentiated cells (130). Intense enzyme synthesis has been recently shown to be a metabolic characteristic of the villous epithelium (172). Activities for alkaline and acid phosphatase, esterase, adenosine triphosphatase, and succinic dehydrogenase were strongly present in the chief cells on the villi of human jejunum, as demonstrated by histochemical methods. Therefore, intense intracellular enzyme synthesis is characteristic of these differentiated epithelial cells and indicates their high metabolic activity. The increased enzyme synthesis which occurs in the normal chief cells after they leave the crypts is accompanied by changes in cytoplasmic ribonucleic acid (RNA) as well as in their morphology. Cytoplasmic basophilia attributable to RNA is intense and diffuse in the crypt cells, but becomes less intense and localized to the cell apices of the

* The authors gratefully acknowledge their collaboration with Drs. H. A. Padykula and A. J. Ladman of the Department of Anatomy, Harvard Medical School, in these studies.

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Increased mitoses of epithelial cells have been noted in nontropical

sprue (172). Present evidence is not adequate to determine if this morphologic appearance reflects increased destruction (shortened survival) or a cellular-biochemical defect in the rate of proliferation. In any event, until more histochemical information is available, these morphologic observations can be attributed in a general fashion to

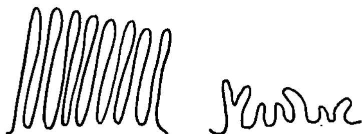


FIG. 3.—Schematic representation of microvilli (striate border) of normal columnar cell *(left)* and its irregular pattern in nontropical sprue *(right)*.

changes in maturation. Whether the increased mitotic activity is associated with inflammatory responses, and/or a biochemical lesion, is unknown. Changes in the lamina propria mucosa, consisting of increased numbers of plasma cells, lymphocytes, and eosinophils, are compatible with either concept. The clinical remissions observed in nontropical sprue patients following a gluten-free diet suggests that the gluten peptide may aggravate an intrinsic mucosal disorder (56). Further studies are necessary to clarify the long-term effects of therapy, as well as the specificity of the lesion. The role of nutritional deficiencies and bacteria should be assessed with regard to the abnormal histology.

TROPICAL SPRUE

ETIOLOGY.—The historic medical interest in sprue was derived from observations of patients with steatorrhea by British and Dutch physicians in tropical areas. The frequency of megaloblastic anemia among the patients in the Caribbean has oriented investigation toward this secondary hematologic complication (173). Although oral folic acid therapy ameliorates the macrocytic anemia, it may improve but not eradicate the malabsorption defect (168). The patients' response to folic acid cannot be attributed to nutritional needs, since tissue levels of folic acid are not severely depleted (43). In fact, since normal body stores of folic acid may not exceed 10 mg. (45), the daily administration of 5 to 10 mg. of folic acid may be considered a pharmacologic treatment. The untreated sprue patient has adequate folic acid cofactors to allow the conversion of glycine to serine (40, 42). However, such

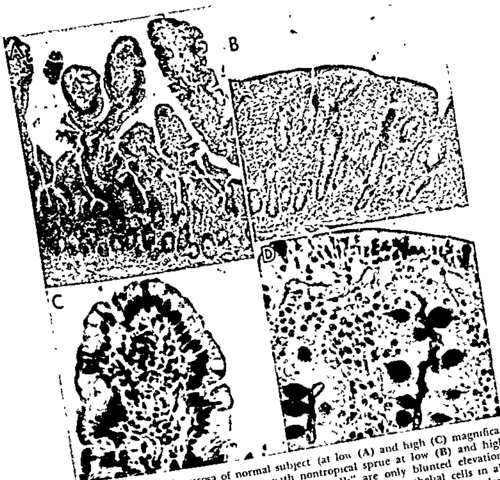


PLATE 1.—Jejunal mucosa of normal subject (at low (A) and high (C) magnifications contrasted with that of patient with nontropical sprue at low (B) and high (D) magnifications. In nontropical sprue (B), "villi" are only blunted elevations above an apparently widened layer of crypts of Lieberkuhn; epithelial cells in abnormal mucosa (D) are generally lower in height and nuclei have lost the orderly location present in normal mucosal cells (C). Typical goblet cells are infrequent on luminal surface of the abnormal villi This is emphasized in photomicrograph D, where mucus appears dark due to staining with the periodic acid–Schiff technic.



PLATE 2.—Jejunal biopsy specimen from patient with early tropical sprue (Stage I). Full length of villi visible, although they are wide and blunted. Ratio of villous length to crypt depth similar to normal (Plate 1A). Note difference between these early mucosal changes and the more advanced ones of nontropical sprue (Plate 1B). (Photomicrograph kindly furnished by Dr. C. E. Butterworth.)

patients excrete excess amounts of formiminoglutamic acid in the urine, suggesting an impaired function of a "transferase" in utilization of tetrahydrofolic acid (45). Large doses of folic acid may therapeutically enhance (mass action) the formation of folinic acid as the final active biologic agent.

There is no adequate etiologic explanation for the sudden onset of malabsorption. Previous efforts to incriminate an infectious agent have not been rewarding (123). No satisfactory isolation of bacteria in the active absorptive area of the upper small bowel has been achieved by aspiration through sterile oral catheters localized in the jejunum, or lavage of selected bowel areas at laparotomy (11, 132). Nevertheless, treatment of tropical sprue patients with antibacterial agents (sulfonamides and antibiotics) has allowed weight gain and caused steatorrhea to disappear (41, 76). Since many patients with tropical sprue experience spontaneous remissions, this therapy may only lessen the interval of symptoms by eliminating excessive bacteria from the ileum and colon. Frazer (71) proposed that a luxuriant bacterial flora could compete for nutritional factors, while migration of colon bacteria into the ileum could vie for absorption of B_{12}. There are no data to associate a viral etiology with tropical sprue, but a "viral" enteritis or infectious diarrhea often precedes the onset of sprue symptoms (84).

French (75) wondered whether rancid fats might be an etiologic factor, since clinicians have noted a decrease of sprue in Hong Kong with the introduction of refrigeration. He has commented on the predominance of sprue in tropical areas where unsaturated fats form the dietary mainstay.

The clinical and laboratory manifestations observed are related to the duration of the impaired function of the small bowel (140). In the early period of malabsorption, symptoms are related to asthenia from electrolyte loss (55). The rapidity of onset of nutritional deficiencies depends on the patient's nutrition prior to impaired absorption. After a hurricane in Puerto Rico in 1932, a high incidence of sprue with macrocytic (megaloblastic) anemia was observed in patients with poor nutrition (148, 149). Significantly, progressive economic improvement in Puerto Rico has decreased the frequency of tropical sprue with megaloblastic anemia.

PATHOLOGY.—Observations derived from bowel mucosa obtained at laparotomy or from aspiration tube biopsy are available for cytologic study (38, 39, 129, 164).

Cytologic changes in the small bowel mucosa have been noted at the onset of tropical sprue (Stage I). Plate 2 shows a biopsy specimen obtained from the jejunum of a military patient 10 days after the onset

of symptoms. The mucosa already contained thickened plump villi with disorganization of the columnar cells and plasma cell eosinophils, and granulocytic infiltration of the lamina propria. These mucosal alterations developed without anemia (hemoglobin, 16 Gm. per 100 cc.) and long before vitamin depletion. After this short interval of diarrhea, the absorption of D-xylose, vitamin A, and butter fat was markedly impaired and the x-ray pattern of the small bowel revealed segmentation and flocculation. Possibly, the early changes in the mucosa are necessary to impair absorption of foodstuffs and initiate the symptoms of diarrhea, lassitude, and weight loss. While this patient had a symptomatic response to folic acid therapy, the process would perhaps have been self-limited upon return to the temperate zone. We do not know whether the mucosa will revert to normal during remission if early treatment is initiated in Stage I of this disorder.

In patients with progressive nutritional depletion initiating the onset of megaloblastic bone marrow changes, the mucosal changes are accentuated, as shown in Plate 2 (15, 38). The villi are more blunted and fused, with a relative increase in the crypt cell depth. Associated with the villous abnormalities are profound alterations of the columnar cells. Instead of having an elongated rectangular shape, they are flattened and more cuboidal in outline. Some areas of the blunted villi at the luminal area appear to be denuded of epithelium (100). There is a disorderly arrangement in the normal palisades of orderly rows of cells, with lack of definition between cell borders. Their nuclei vary in size. Numerous pyknotic nuclei are associated with leukocytic infiltration of the mucosa. Goblet cells are increased along the borders of the blunted villi. The microvilli are irregularly shaped and more sparse (100). The more severe cytologic changes are similar to the alterations noted in nontropical sprue (Plate 1). The lamina propria is edematous and increased leukocytes and plasma cells appear between engorged capillaries. With folic acid therapy, the columnar cells regain a more orderly palisade appearance, but the shape and size of the villi remain defective. The cytologic alterations have persisted despite 5 to 10 years of folic acid treatment (38). While the orderly sequence of mucosal changes has not been completely studied by biopsy technic, the initial changes within 10 days of onset of symptoms suggest that the bowel response to the offending agent is rapid and irreversible. The columnar cells may reassume a normal appearance with vitamin replacement (B_{12} and/or folic acid), but the villi remain distorted. With the permanent alteration of the villi, there is a marked decrease in the surface area for absorption. Butterworth and Perez-Santiago (38) have estimated that these alterations may decrease sur-

face area for absorption by 80 per cent. Also, the shortened villi may have less undulating motion to maintain contact with specific food components in the bowel lumen.

Differentiation of Tropical and Nontropical Sprue

Despite the etiologic factors in these disorders, can a pattern of clinical symptoms, pathology, and therapy help to differentiate two distinct entities? The following comparisons may be helpful in orienting the clinician in this problem, for the past decade has seen striking therapeutic measures utilized which tend to separate the disorders more clearly than was previously possible.

Laboratory data.—With prolonged malabsorption, the same final pattern of nutritional deficiency may be found in both syndromes. Hence, persistent malabsorption for months or years in tropical sprue patients will manifest all of the absorption defects seen in nontropical sprue or celiac disease patients in whom malabsorption has probably been present for many years before diagnosis. Since the tropical sprue patient usually can detect the onset of bowel symptoms, the illness may be of shorter duration. Therefore, with less time to deplete body reserves, some measurements of altered small bowel function may be changed only slightly.

Symptoms of calcium depletion and hypoprothrombinemia are infrequently seen in tropical sprue. With regard to diagnostic procedures, no laboratory measurement or test will separate the two disorders. The enhanced blood levels of glutamine after oral ingestion of gliadin may be helpful in establishing a diagnosis of childhood or adult celiac disease.

Onset.—Tropical sprue usually appears in adult life. In tropical climates, careful recognition must be given to the frequency of childhood diarrhea which has been attributed to parasitic disease. Indeed, with adequate specific therapy, the diarrhea disappears. However, careful correlative studies in later life have not been documented to exclude any recurrence. For the present, tropical sprue may be limited to adults in view of the age of onset.

In contrast, enough time has now elapsed since the clinical separation of celiac disease from mucoviscidosis to indicate that a large percentage of adult patients with nontropical sprue have a childhood history of disturbed bowel function. With the advent of more complete health records, a better correlation may be anticipated between childhood and adult celiac disease. In some patients, a tolerance to the spe-

cific irritant (gluten) appears to develop during childhood, only to recur in adult life. Studies of growth and physical function would indicate that absence of diarrhea does not signify full physiologic development, for many asymptomatic adolescent patients with a previous diagnosis of celiac disease have had some evidence of malabsorption by laboratory criteria and impaired growth (88).

Pathologic changes.—The mucosal lesion in both disorders may be similar according to the biopsy technics recently available. Certain changes in the two disorders are of interest as specimens are compared.

Degree of villous change.—In most instances, the tropical sprue mucosa has more residual villi present. In fact, clumps of relatively normal villi may be seen among the areas of distorted morphology. While the villi may be bulbous, blunted or fused, at least their outline can be discerned. In contrast, in the nontropical sprue child patient or adult celiac patient more advanced changes in the villi are seen, with little residual evidence of the single villus identified. The villi are blunter and broader based, possibly elevated above the crypt level only a third as high as in tropical sprue.

Microvilli.—The untreated tropical sprue patient has distorted microvilli, with blunting and fusing. Similar changes have been observed in electron micrographs of nontropical sprue patients. With vitamin therapy, there is a more orderly maturation of columnar epithelium, and less distortion of the microvilli in the tropical sprue epithelium. The nontropical sprue patients observed after 1 year of gluten-free diet have marked distortion of microvilli. These persistent changes may correlate with the continued alterations in the columnar cell. More observations will be necessary to determine whether these changes will persist if dietary gluten is excluded for many years. If isolated crypts retain the capacity to proliferate a normal precursor, some bowel areas may show a more normal columnar cell and microvilli.

The present observations would suggest that both syndromes may have irreversible villous changes. Treatment of tropical sprue will improve the cytology of the columnar epithelium rapidly if the disease is of short duration. Gluten exclusion will shift the columnar cell cytology toward a more normal appearance, but the chronicity of nontropical sprue indicates that the epithelial lesion will remain abnormal despite indefinite therapy.

Response to therapy. *Antibiotics.*—Tropical sprue patients have responded to antibiotics with loss of steatorrhea and weight gain. Similar responses have not been noted in nontropical sprue.

Folic acid.—In both disorders, oral absorption of folic acid is impaired before therapy (89). The oral administration of folic acid in

pharmacologic doses (5 to 15 mg. daily) will ameliorate hematologic disorders (megaloblastic bone marrow) in both disorders. Possibly, the nontropical-sprue patient responds more efficiently if large doses of ascorbic acid are given with the folic acid. Folic acid will improve clinical symptoms and cause abnormal laboratory measurements to revert to normal in the early phases of tropical sprue, even in the absence of anemia. In Stage III of the disease, folic acid lessens steatorrhea and improves the laboratory indices of malabsorption. In most instances, some degree of malabsorption persists. The amelioration of the anemia of nontropical sprue patients may improve clinical symptoms, but vitamin therapy does not match the salutory results observed in tropical sprue.

After oral folic acid therapy, the tropical sprue patient is able to absorb folic acid in a normal fashion. In a few observations, antibiotic therapy has also caused folic acid absorption to revert to normal (49). With gluten-free diets, the nontropical sprue patient experiences partial improvement, but folic acid absorption never returns to the normal range noted in tropical sprue (60). The abnormality of gliadin metabolism in the epithelium may be related to the continued malabsorption of folic acid (57).

Gluten-free diet.—Limited observations in tropical sprue patients suggest that gluten exclusion does not alter the clinical manifestations. However, the duration of the dietary control has not been defined. Since the program must be maintained for months (200 days), studies have probably been inadequate. These negative responses are in marked contrast to the high percentage of clinical improvement noted in childhood and adult celiac disease. Steatorrhea disappears, the absorption test results return almost to normal, and the nontropical sprue patients may experience hematologic improvement. The therapeutic "yield" in nontropical sprue depends on the diligence of the physician in supervising the diet. While the gliadin component has been the most frequent etiologic offending agent in nontropical sprue, other peptide components may be discovered.

Before the gluten-free diet came into use, corticoids were the most useful agent in the treatment of nontropical sprue. Therapy is associated with rapid cessation of steatorrhea, weight gain, and disappearance of abdominal symptoms of cramping and distension (53a). Although the clinical improvement has been attributed to a more efficient intestinal absorption, some effects may be related to systemic manifestations (54). Corticoids (cortisone acetate or prednisone) have a useful clinical role in the initial treatment of the severely debilitated patient. There are no adequate studies to define the influence of adrenal hormones in tropical sprue.

"SECONDARY SPRUE" SYNDROMES

It is now re-emphasized that morphology alone cannot establish a diagnosis of tropical or nontropical sprue. However, small intestinal mucosal lesions pathognomonic of various diseases have been associated with impaired intestinal absorption. These other diseases may closely simulate sprue for limited periods of time.

Collagen Disease and Scleroderma

Obstructive absorption from the small bowel may be the final phase of collagen tissue changes and vasculitis. With the loss of vascular integrity, the supporting lamina propria and columnar mucosa flatten, with loss of villi (153). Even if the mucosal membrane continues to maintain a normal morphology of the columnar cells, the surface area available for absorption is markedly diminished. The submucosal tissue evidences a diffuse vasculitis, with thrombosis of venules, impairing absorption through the portal circulation. The occlusion of the arterioles may alter metabolic function of the epithelium, as noted in patients with transient obstruction of the major mesenteric arterial vessels (110). In this instance, however, the ischemia is permanent, with no possibility of eventual repair of the cellular dynamics. The vasculitis also causes increased fibrosis in the muscularis and loss of muscle mass (1). These alterations impair motility and allow unusual dilatation of the bowel lumen, more so in the proximal than distal small bowel (125).

Amyloid Disease

The presence of amyloid tissue in the lamina propria may be associated with impaired absorption of fats as well as other nutrients; in fact, a histologic biopsy is often needed to clarify the exact diagnosis. In most instances, the columnar epithelium appears normal cytologically, although the villi may be distended, widened, and blunted by deposition of amyloid in the blood vessel walls and lamina propria. There are no characteristic physiologic alterations to suggest amyloid disease of the bowel. The diagnosis may be suspected if other amyloid infiltrates are observed.

Lymphoma

The invasion of the entire small bowel by lymphosarcoma or Hodgkin's tumor has been reported as a mechanism for steatorrhea. Results of all of the classic absorptive studies may be abnormal. Sleisenger *et al.*

(165) have reported *that lymphoma represented 20 per cent of the* cases of nontropical sprue. With the varied biopsy technics now available, a histologic diagnosis should be obtained in all cases of malabsorption. The columnar epithelium has not been studied in fresh specimens, but no marked changes have been found in postmortem studies. For the most part, the tumor may invade the lamina propria as an "obstructive" factor. The lacteals may be obstructed from disease in the regional lymph nodes, while an associated amyloid deposit may be the more prominent histologic evidence in the lamina propria.

WHIPPLE'S DISEASE

The continued accumulation of clinical data has suggested that this disease represents a systemic disorder, possibly a metabolic error associated with familial occurrence (97). The deposition of glycoproteins in the macrophages of subcutaneous lymph nodes has facilitated the diagnosis (143, 169). The accumulation of macrophages containing an aldehyde material (positive reaction to periodic acid–Schiff staining) in the lamina propria is associated with a malabsorption syndrome (109). Reactions to oral tolerance tests and x-ray pattern of the small bowel may show varying degrees of abnormality and steatorrhea may be present. Iron deficiency is more often present than megaloblastic alterations of the bone marrow.

The columnar cells are not involved in this disorder. The mucosal pattern reveals an orderly palisade appearance of the epithelium from the crypts to the absorptive surface. The villi are shortened and blunted, reflecting distention of the lamina propria by the phagocytic "foam" cells filled with the mucopolysaccharide and by dilatation of the lacteals. These histologic changes would suggest that the absorptive cells can actively transfer foodstuffs. The rate of transfer is impeded by the distention of the lacteals and by the changed vascularity due to engorgement of the submucosal area. The onset of small bowel dysfunction is gradual and related to the slow infiltration of the macrophage aggregations in the lamina propria. The diagnosis is made conclusively by lymph node or bowel tissue obtained at laparotomy or by intraluminal tube biopsy (48). Prolonged invasion, vascular alterations, and impaired lacteal drainage defeat all efforts to improve nutritional defects (97, 145).

Some patients have exhibited improvement of malabsorption after corticoid therapy (109). Two mechanisms may possibly explain this gratifying clinical response: *(1)* decreased deposition of the circulating mucoprotein by lessened production after corticoid therapy; and *(2)*

improved drainage of distended lacteals by lympholysis and decreased macrophages in the mesenteric lymph nodes allowing better lymphatic circulation. However, if the changes are extensive, the process is irreversible and no response to corticoids should be anticipated (97).

COMMENTS

A variety of clinical measures have been devised to reveal impaired intestinal absorption of foodstuffs. The results of these tests give some information concerning rate or amount of absorption as compared to normal. However, other factors may influence the over-all results of these tests. For instance, blood levels of glucose are affected by the ability of the liver to form glycogen. Knowledge from animal studies was presented in order to demonstrate that intestinal absorption of some substances may occur by "active" mechanisms. Glucose is absorbed in this manner, although no absorptive work is necessary for the transport of other substances, as described earlier.

By analogy with animal studies, "active" absorption may be performed by the human intestine. At present, there is no clinical method for quantitating singly the small intestine's ability for absorptive work; that is, transport against an "uphill" electrochemical gradient. It is likely that development of a clinical method for this determination would allow significant advances in our knowledge of diseases of the small intestine. A mucosal lesion is present in the small intestine of patients with the sprue syndrome which may eventually be proved to account for the defective intestinal absorption. Although the absorptive function of the small intestinal mucosa has been stressed in this review, it must be recognized that there are other intestinal derangements (such as altered motility and secretion) in the sprue patient which may be important in malabsorption.

It is possible for a decreased dietary intake or an increased bodily need to cause deficiency of an essential foodstuff. Malabsorption in itself may result in a nutritional deficiency. Clinical improvement in tropical sprue following folic acid therapy might be attributed to the alleviation or removal of any of these three possibilities. Laboratory data and clinical observations suggest that inadequate intake and malabsorption of folic acid may not be associated with the onset of tropical sprue. The abnormal absorption of gluten in nontropical sprue may be related to a derangement in the intermediary metabolism of folic acid. Malabsorption of vitamins and food substances may be related to congenital as well as acquired defects in cellular chemical pathways which might function more normally at very high concentrations of these nutrients.

Improved small bowel function following corticoid therapy suggests that the hormone influences biochemical pathways including those which are involved in inflammatory or allergic processes. Tools are now available for more precise evaluation of the role of absolute or relative deficiencies in the pathogenesis of sprue. These should give a better understanding of deficiency as a contributing etiologic factor in cases of altered intestinal absorption.

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Clinical Phonocardiography

Graphic Analysis of Clinical Auscultation

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CONCOMITANTLY WITH the advent of cardiac surgery some 20 years ago, a rapid development of cardiac diagnostic technics occurred. Interest in the art of clinical auscultation has also revived. Although its foundations had been well established, great advances have been made recently through intensive correlative studies and direct demonstration of the physiologic mechanisms involved. The availability of precise anatomic information provided by cardiac surgery, angiocardiography, cardiac catheterization, and postmortem examination has contributed to our improved appreciation and application of cardiac auscultation.

The introduction of the string galvanometer by Einthoven (37) made possible the recording of cardiac sounds and murmurs. Indeed, his phonocardiograms are superbly clear and technically perfect. But as in electrocardiography, our technical demands have grown more sophisticated with regard to the scope and ease of instrumentation, and we no longer are satisfied with string galvanometer technics. Now, clinical phonocardiography provides a permanent, objective record to supplement the fleeting impressions of auscultation.

Clinical auscultation and clinical phonocardiography *should* supplement each other, much as roentgenography supplements physical examination of the lungs. The highly skilled and experienced cardiologist will feel the need for such records less often than the student and aspiring master of the stethoscope. The musical or nonmusical character, the frequency, composition, and variation from point to point can best be assessed by direct auscultation, whereas the time relation

of sounds to electric and hemodynamic events can only be analyzed by means of the phonocardiogram. Simultaneous recording of sounds and electrocardiographic, pulse, and pressure tracings documents cardiac dynamics precisely, and provides accurate timing of murmurs in relation to sound and cardiac cycle. The teaching value of phonocardiography almost exceeds its clinical value. The analysis of the graphic tracings gives the student familiarity with the fundamental mechanisms of the heart beat. It also may clarify auscultatory findings which are hard to interpret.

The recording of heart sounds and murmurs on magnetic tape is useful if they are simultaneously inscribed along with electrocardiographic and pulse tracings. Frequency-modulation (FM) equipment is required for this, but it is very expensive and far beyond the budgets of most laboratories. So far, only McKusick has used this technic. The use of nonmodulated tape recorders in medical schools is reported to have some importance in introducing medical students to auscultation (17). In our opinion, auscultation has to be taught at the bedside, and we therefore believe that conventional tape recorders, no matter how "Hi-Fi," are not needed for any purposes other than demonstration.

Spectral phonocardiography, based on the idea of the Bell Telephone Corporation's "Speech Visualizer" and applied to the recording of heart sounds by McKusick, presents an amplitude-frequency graph. The admirable studies of McKusick and associates (70) have shown the wide range of applicability. We believe that a multiple filter technic is preferable, although either technic will probably yield similar results in the hands of experienced investigators.

Microphones and preamplifiers of the recording system have to be matched, an obvious fact not always observed. The response of the recording system should be from 20 to 1,000 counts per second (c.p.s.) with adequate provisions to eliminate the low frequency at will and to an adequate degree.

The following specifications would be desirable in heart-sound recording apparatus: frequency range from 15-20 to 1,000 c.p.s., with an essentially linear response of microphone–amplifier system over most of the range (30–800). Several heart sound channels, 2 and preferably 3, for either simultaneous recording from 2 or 3 different locations, or for the simultaneous recording of 2 or 3 different filter ranges; provisions for simultaneous recording of ECGs, pulse and pressure tracings; a cathode ray oscilloscope for monitoring and adjustment of graphs, might prove desirable. The design of filters should have the characteristics suggested by Mannheimer (72), in octave steps with low-frequency attenuation of adequate steepness (18–24 decibels).

NORMAL HEART SOUNDS: THEIR GENESIS AND CHARACTERISTICS

First Heart Sound (Plate 1, *A*)

The mechanism of production of the first heart sound has been the subject of considerable investigation and controversy. Evidence has been presented that atrial contraction, muscular vibrations, atrioventricular (A–V) valve closure, and semilunar valve opening all contribute to the many components of the first sound (62, 64, 89, 91, 118). Dock (31–34) believes that only valvular factors i.e., A–V valve closure, are responsible for the genesis of the first sound. The consensus of most investigators favors the concept of a multiple origin for the genesis of the first sound, but that the audible portion is due almost solely to the closure of the A–V valves. When the various components of the first sound are analyzed, however, the smaller vibrations before and after the major ones have been ascribed to other factors. The *initial low* amplitude vibrations have been ascribed to atrial contraction (26, 89, 91); but they have also been observed in patients with atrial fibrillation (28), and have been ascribed to tension of the ventricles prior to mitral valve closure (65, 86, 103, 104). However, Braunwald and Morrow (12) believe that the opening vibrations of the first heart sound are valvular. They demonstrated that in mitral stenosis, when the onset of the first sound is delayed, the earliest vibrations occur after onset of the rise in the left ventricular pressure curve and hence *after* ventricular contraction has begun.

More recently, Dock (34) has presented evidence that very large forces are necessary to evoke audible sounds from strips of muscle, and that such a magnitude of force does not occur in living animals. Moreover, attenuation of heart sounds in air and fluid is great; 70 to 95 per cent of the sound intensity generated by closure of the A–V valve is lost by attenuation through the blood and the ventricular and chest walls even when the apex is touching the chest wall and thereby eliminating intensity loss through air. In addition, short fibers (semilunar cusps and mitral curtain to line of adhesion), when tensed, give high pitched sounds, while long fibers (A–V system from papillary muscle to annulus) give low-pitched sounds.

The central phase of the first sound is comprised of 2 to 4 large amplitude vibrations generally attributed to closure of the mitral and tricuspid valves in that order (50, 65, 93). Luisada *et al.* (65) have presented evidence that when the first sound complex is comprised of 4 large amplitude vibrations the latter 2 are caused by pulmonary and

aortic valve opening in that order, since their timing corresponds with the onset of the pulmonary and aortic artery pressure curves in both dog and man.

Audible splitting of the first sound due to asynchronous ventricular contraction may be normal, but it is usually narrow, the interval between the tricuspid and mitral valve closure being 0.02 to 0.03 second (50) (Plate 2, *B*). Abnormally wide splitting occurs in complete right bundle-branch block due to a delay in the onset of right ventricular ejection and tricuspid valve closure (11, 13, 50) (Plate 3, *D*). In left bundle-branch block, there is ordinarily no delay in the onset of left ventricular contraction and hence splitting of the first sound is not a feature (11) (Plate 3, *B*).

In mitral stenosis there is a delay in onset of the mitral component of the first sound (46) (Plate 4). The delay may be such that the mitral closure follows the tricuspid rather than precedes it (24, 45, 114), but audible splitting is uncommon.

INTENSITY OF FIRST HEART SOUND.—Several factors are important in the determination of the intensity of the first sound. The most important is probably the position of the A–V valves at the onset of ventricular contraction (59, 68, 119). It has been shown that there is an inverse relation between the intensity of the first sound and the preceding P–R interval (119), and, in mitral stenosis with atrial fibrillation, with the length of the preceding diastole. When the A–V valves are widely open at the onset of ventricular contraction so that they must traverse a wide arc in order to close, the first sound is loud. This occurs in mitral stenosis due to high left atrial pressure; in conditions with a short P–R interval, in which case atrial contraction just preceding ventricular contraction opens the A–V valves wider; and in atrial fibrillation or premature contractions, in which the preceding diastole is short so that contraction occurs during the rapid filling phase when the A–V valves are widely open. An exception is the Wolff-Parkinson-White syndrome, in which despite a short P–R interval the first sound is not accentuated (Plate 2, *C*). Conversely, the first sound is diminished in intensity when there is mitral insufficiency and the mitral valve never fully closes, when the P–R interval is long or in atrial fibrillation, or when the preceding diastole is long and filling is complete before systole begins. Ectopic beats may cause first sounds louder than in the normal and forceful beat that follows (because early inflow is reversed), and earlier ectopic beats may cause no first sound because the valves have not begun to move from their systolic position. A thick chest wall, emphysema, or pericardial effusions

make the sound soft. Anemia, thyrotoxicosis, and tachycardia increase its intensity (59, 68, 119). Myocardial failure or infarction often causes a weak, muffled, soft first heart sound. This has been ascribed to altered contraction of a weakened myocardium. However, it may be due to rapid ending of diastolic or presystolic filling when atrial pressure is elevated by ventricular injury.

The first sound occurs from 0.02 to 0.06 second after the onset of the QRS complex. This is known as the Q-1 interval and is an important measurement. It is prolonged in mitral stenosis but is not pathognomonic of this condition, since it also has been observed in hypertension.

SECOND HEART SOUND (Plate 1)

Closure of the semilunar valves is probably the only event responsible for the second sound, although Luisada (61) believes that opening of the A-V valves plays a role in the genesis of the second sound complex. The separation into aortic and pulmonary components is of fundamental importance in the understanding of the genesis of the second sound. Normally, there is asynchrony in the closure of the semilunar valves with the aortic preceding the pulmonary component (50, 55, 65) (Plate 1, *A*). On inspiration, due to an increased right ventricular stroke volume, the right ventricular ejection period lengthens and there is a further delay in pulmonary closure so that splitting of up to 0.08 second may normally occur (50, 55). Conversely, on expiration, the splitting normally narrows and hence one should listen for abnormal splitting during this period (53) (Plate 5, *C*). Wide splitting occurs when resistance to left ventricular ejection is decreased and A_2 is early, or when pulmonary closure is delayed due to a lag in right ventricular conduction. Such splitting occurs in complete right bundle-branch block (Plate 3, *D*), or in increased resistance to right ventricular ejection or increased right ventricular stroke volume due to large left-to-right shunts. Wide splitting occurs with atrial septal defect (Plate 6), occasionally with ventricular septal defects, and with pulmonary stenosis (54, 57) (Plate 7, *D*).

Paradoxic splitting of the second sound is the term used when the aortic component follows rather than precedes the pulmonary component. It has been observed in the following conditions (42): *(1)* when left ventricular ejection is prolonged due to increased resistance to ejection, as in aortic stenosis and systemic hypertension; *(2)* when there is conduction delay in the left ventricle, i.e., in left bundle-branch block; and *(3)* when there is diastolic overfilling of the left ven-

tricle, as in patent ductus arteriosus with left-to-right shunt (Plate 3, *A–C*). It can be detected clinically and on the phonocardiogram when on inspiration the split second sound becomes narrow or disappears rather than the converse.

The intensity of the aortic and pulmonary components of the second sound is increased with hypertension or increased flow in the systemic and pulmonary circuits and decreased with stenosis of the valves or emphysema. Phonocardiography has taught us a great deal about the second sound which has been useful clinically. Positive identification of the aortic component can be made by the simultaneous recording of the carotid artery pulse. The aortic closure corresponds to the dicrotic notch of the carotid tracing; however, a 0.01 to 0.04 second delay in the carotid pulse must be allowed, due to a lag in the recording system.

Third Heart Sound (Ventricular Filling Sound) (Plates 1 and 5)

A low-pitched sound may occur approximately 0.14 second after onset of the second sound. When timed with the jugular venous pulse, it occurs on the steep descent of the V wave and hence corresponds to rapid ventricular filling.

Although all the investigators generally agree that the physiologic third sound corresponds to rapid ventricular filling, they disagree on the genesis of the sound. Dock and associates (32, 35) believe the sound to be caused by valve movement, whereas Orias and Braun-Menendez (89) and Wolferth and Margolies (120) support the theory of a muscular origin of this sound. It is commonly heard in normal man below the age of 40. Factors favoring rapid filling, such as mitral regurgitation and left ventricular failure with a tachycardia, often are associated with a prominent third sound. It is important to differentiate the normal occurrence of the third sound from its occurrence in abnormal states, from splitting of the second sound, and from the opening snap of the A–V valves. The third sound is dull, low-pitched, and fairly well restricted to the apical region, and is best heard with the bell of the stethoscope and in full expiration. The opening snap from which it must be differentiated is sharper, louder, and, although best heard just inside the apex, is usually present over the entire precordium (45). Splitting of the second sound is best heard over the pulmonary area in full inspiration, and only at the apex when the pulmonary component is unusually loud.

Fourth Heart Sound (Atrial Sound) (Plate 1, *A*)

Normally, the atrial sound is probably never audible, and, when present, probably signifies increased resistance to ventricular filling (119). It is most often present in systemic hypertension, and, rarely, in aortic valvular disease when there is left ventricular hypertrophy. It may become accentuated and audible with myocardial infarction, but is not invariably associated with cardiac failure. Weitzman (113) never heard it in over 100 healthy subjects. However, atrial sounds have been recorded phonocardiographically in up to 85 per cent of normal subjects by Orias and Braun-Menendez (89).

Occasionally, with complete or partial heart block and atrial flutter, the atrial sound is audible (25), but more often it is recorded only on the phonocardiogram. It is a sound of low pitch and low intensity. It may be distinctly separate from or merge with the first sound, depending on the P–R interval.

The *importance of the atrial sound lies in the fact that it is never* heard in normal subjects and that when audible it must be differentiated from a split first sound, an ejection sound, and a summation gallop. Splitting of the first sound is usually narrow (0.03 second) and both components are sharp. There is a wider (usually, 0.08 second) gap between the atrial sound (which is low pitched) and the first sound.

Fifth Heart Sound

This has been described by Calo (18) and Luisada and Mautner (63). It occurs after the third sound and before atrial contraction. There are no important hemodynamic events occurring during this period and if such a sound exists it is of little clinical importance and is probably never audible.

A–V Valve Opening Sounds (Plate 4)

Opening of the tricuspid and mitral valves is normally silent. In the phonocardiogram, low-frequency vibrations following the second sound can often be seen, and have been attributed to the opening of the A–V valves (65). With mitral or tricuspid stenosis, the opening becomes audible as a sharp snapping sound. On the phonocardiogram, *its timing corresponds more or less to the peak of the V wave of the* jugular pulse. The mitral snap usually occurs 0.07 second (0.03–0.14) after the onset of the second sound (74, 80). Its presence implies a

tricle, as in patent ductus arteriosus with left-to-right shunt (Plate 3, *A–C*). It can be detected clinically and on the phonocardiogram when on inspiration the split second sound becomes narrow or disappears rather than the converse.

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other hand, feel that valve opening is responsible for the early click in these conditions. Usually, a murmur is present. The early click is a *definitely abnormal finding in these instances.*

MIDSYSTOLIC AND LATE SOUNDS (Plate 8, *A* and *B*).—These are grouped together, as their significance is similar and they are more commonly due to extracardiac conditions. Of 146 patients with systolic clicks in the series of Minhas and Gasul (77), only 17 occurred in mid- or late systole. Most of their 146 patients had congenital heart disease and early basal clicks.

Pleuropericardial adhesions, pulmonary disease, pneumothorax, and deformities of the chest wall often are associated with mid- and late systolic sounds. One of the features of these sounds is their variability in timing from beat to beat, and their presence often depends on a particular phase of respiration or body position. In contrast, the early ejection sounds are more or less constant in timing and presence.

Mid- and late systolic sounds are best heard at the apex or mid-precordium. Not infrequently, a murmur which is also extracardiac follows the sound and extends into diastole.

These sounds must be differentiated from splitting of the second sound, third sounds, opening snap, and diastolic gallops. Not infrequently, an erroneous diagnosis of heart disease is made due to the misinterpretation of systolic sounds, especially the late click. Although the experienced physician can interpret these clinically, the phono*cardiogram has proved to be a useful aid in uncertain situations.*

DIASTOLIC TRIPLE RHYTHMS (GALLOPS)
(Plates 10 and 11)

These can be divided into three types: the protodiastolic (ventricular filling), the presystolic (atrial), and the summation gallop. They are accentuations of normally occurring but inaudible hemodynamic events (35, 64, 120).

PROTODIASTOLIC GALLOP (Plate 11).—When ventricular filling becomes abnormally rapid, an early diastolic gallop occurs. Tachycardia, with a shortening of diastolic filling, therefore favors this sound. Identical in timing with the physiologic third sound, the ventricular filling gallop is always considered abnormal in patients over the age of 40. The physiologic third heart sound shows a marked respiratory variation, whereas a protodiastolic gallop shows little variation. It is low pitched but may become very loud, and although usually best heard at or just medial to the apex we have recorded it at Erb's area and at the base of the heart. It occurs generally 0.14 second after the second

relatively pliable or mobile valve, but does not exclude significant regurgitation. It has been shown to be loudest inside the apex and may be audible over the entire precordium, and, when very loud, over the back. The opening snap may be the loudest sound in the cardiac cycle and be palpable as well as audible. The quality, earlier appearance, and radiation serve to differentiate it from the low-pitched third sound which occurs later and is fairly restricted to the apex. Wide splitting of the second sound is differentiated from the opening snap by the absence of the former when listening over the apex, and in mitral stenosis by the demonstration in the pulmonary area of both the splitting and opening snap on full inspiration. Rivero Carvallo (95) and Kossmann (48) have described the tricuspid opening snap which occurs later and is softer than the invariably associated mitral snap. The tricuspid opening snap has also been recorded in atrial septal defect (53, 68); the mitral opening snap, with high flows across the mitral valve in patent ductus arteriosus and in ventricular septal defect (68).

Systolic Sounds

Triple rhythms (Plate 8, *A* and *B*).—An extra sound may occur in systole as a result of several conditions. It may be heard in early, mid-, or late systole, and be associated with a murmur. Such sounds have been erroneously called gallops, but the quality, cadence, and genesis of these sounds are so different from true diastolic gallops that we feel the term systolic gallop should be dropped. The subject has been recently reviewed (8).

Early sound (ejection sound) (Plate 9, *D*).—In the presence of dilatation of the aorta or pulmonary artery, hypertension in the systemic or pulmonary circulation, or stenosis of the aortic or pulmonic valve, there may be an early, high-pitched clicking sound often mistaken for a split first sound. Leatham and co-workers (53, 56, 57) have called this the ejection sound. It is more common in abnormalities of the pulmonary valve and circulation than of the aortic valve and systemic circulation. The sound is best heard at the base of the heart. Leatham and Vogelpoel (56) have demonstrated that the sound occurs on the average of 0.14 second after the QRS complex, 0.07 second after onset of the first sound, and 0.03 second after the rise of the pulmonary artery pressure curve; they therefore concluded that it is due to vibrations of the pulmonary artery during rapid ejection. The intensity decreases with deep inspiration, but the timing is more or less constant. With pulmonary hypertension, the sound is somewhat delayed, and may appear to be more midsystolic. Minhas and Gasul (77), on the

the length of the interval varies. When the previous diastolic interval is short, the interval is usually longer and the first heart sound is generally louder; the probable explanation for this is that with a short diastole the A–V filling gradient is greater, the mitral valve is more widely open, and therefore more time is required to close the valve. Conversely, when the preceding diastole is long, more complete filling of the left ventricle occurs, the left atrial pressure is lowered, and the mitral valve is more closed at the onset of ventricular contraction; as a result, less time is required for complete closure of the mitral valve.

Occasionally, the opposite occurs and the intensity of the first sound as well as the Q-1 interval are proportional to the length of the preceding diastole. The explanation for this phenomenon is unclear. Many factors, however, determine the Q-1 interval; delay in electric conduction, mechanical factors, and degree of mitral valve fibrosis all may influence this interval. Weissler *et al.* (112) reported a prolonged interval in a group of hypertensive patients. Because of a lack of specificity, the wide range of the normal, and the many factors influencing this interval, no great emphasis should be placed on this measurement alone in the evaluation of patients with mitral stenosis.

2-OS INTERVAL.—The time between the onset of the second sound and the opening snap in mitral stenosis is known as the 2-OS interval. It is an expression of the time between closure of the aortic valve and opening of the mitral valve, or isometric relaxation phase. This represents the time of fall of the left ventricular pressure (from the level of the diastolic pressure in the aorta) to that just below the left atrial pressure. Since normally no opening snap is heard, this measurement is significant only in patients with mitral stenosis. Many investigators have correlated this interval with the pulmonary artery or pulmonary capillary pressure (114, 121). When left atrial pressure is high, earlier opening of the mitral valve occurs and the interval is short; the converse is true in mild mitral stenosis with low left atrial pressures. However, in atrial fibrillation, the 2-OS interval varies being proportional to the length of the preceding diastole (Plate 4, *D*). With systemic hypertension, the interval may be prolonged (121).

Wells (114, 116) found a better correlation with the gradient across the mitral valve and mitral valve size (estimated at the time of operation) when the Q-1 interval minus the 2-OS interval (corrected to a constant cycle length) was used than with either of these measurements alone.

Following successful valvulotomy, the 2-OS interval lengthens, indicating that there has been a reduction in the A–V filling gradient.

sound, but may be earlier when tachycardia is present (37, 120). In timing, it corresponds to the descent of the V wave of the jugular pulse. Both occur as an inflection of the apex beat which shows that there is a reversal of motion in the left ventricle.

PRESYSTOLIC GALLOP (Plate 10, *C*).—As previously mentioned, the atrial sound is normally never audible (113). When the P–R interval lengthens, signifying a wider interval between atrial and ventricular contraction, the atrial sound may be heard. With increased resistance to ventricular filling even without prolongation of the P–R interval, the atrial sound may be audible; this has been called the presystolic or atrial gallop. It occurs most commonly in systemic hypertension, after myocardial infarction, myocarditis, and, less often, in aortic stenosis; although always abnormal, it is not invariably associated with ventricular failure (113). Right atrial gallops have been recorded in pulmonary stenosis, pulmonary hypertension (68), and in 1 case of right atrial myxoma.

SUMMATION GALLOP (Plate 10, *B*).—When the diastolic interval is shortened so that the rapid filling period coincides or almost coincides with atrial contraction, the third and atrial sounds may summate into a loud audible gallop. If the third and atrial components can be separated by slowing the heart rate through carotid sinus stimulation, not infrequently the gallop will disappear as the individual components may be inaudible unless they combine (120), or, if each individual component is heard, a quadruple rhythm may occur.

On the phonocardiogram, gallop sounds are best recorded with the low-frequency (stethoscopic) system. They are best audible with the bell of the stethoscope applied lightly to the chest wall at the apex, with the patient recumbent and in expiration.

SOUND INTERVALS

Q-1 INTERVAL.—This interval represents the time between onset of the QRS complex of the ECG and the first major vibration of the first heart sound. The normal interval is 0.055 second, with a range of 0.03 to 0.07 second (112). It was first described as being prolonged in mitral stenosis by Weiss and Joachim in 1911 (111). The interval may be increased to as much as 0.12 second. Several investigators have recently stressed its consistent prolongation in mitral stenosis, and attempts have been made to correlate the degree of prolongation with the severity of the mitral stenosis (29, 46, 114). After successful commissurotomy, the interval may become shorter. In atrial fibrillation,

There is fibrosis, thickening, and roughness of the intima or endocardium at these sites. Vibrations which are caused when the jet stream hits these areas are thought to be responsible for the genesis of murmurs when there is a high-pressure gradient and a high-velocity jet flow through a narrow orifice. Such lesions are rare in cases of relatively slow blood flow across a large orifice (e.g., in mitral stenosis).

FUNCTIONAL (INNOCENT) SYSTOLIC MURMURS (Plate 2, *A* and *B*).—Systolic murmurs not caused by structural abnormalities of the cardiovascular system are so common, especially in infants and children, that their differentiation from organic murmurs is important. At times, such a differentiation may be difficult and the phonocardiogram may be useful because the timing and length of innocent murmurs are fairly characteristic.

The most common type is the pulmonary systolic murmur. It is separated from the first sound by a brief gap; is of medium or high pitch; is musical, soft, early, crescendo-decrescendo; and ends before the second sound (73). It is best heard after exercise and in the supine position. Turbulence from rapid right ventricular ejection is probably responsible for this type of murmur.

A pulmonary systolic murmur has been recorded with the aid of an intracardiac microphone in all subjects undergoing cardiac catheterization. A systolic murmur of at least faint intensity was heard in all 108 children studied by Paulin and Mannheimer (90).

Late systolic apical murmurs are most often innocent, although we have observed this type in mitral regurgitation. Many of them originate with a click and may be extracardiac in origin.

Midsystolic murmurs are the most difficult to differentiate from those due to organic lesions, such as aortic or pulmonary stenosis. However, innocent murmurs are usually not as loud (rarely louder than grade 3 on a scale of 6), are not associated with a thrill, and are rarely as long as the ejection murmurs of stenotic valves.

Conditions which lower blood viscosity (e.g., anemia) or speed the circulation are often associated with functional murmurs, since they disappear when the condition is corrected.

Occasionally, innocent murmurs are very loud and are audible over the entire precordium and even the back. They may be harsh, blowing, or musical, and their significance is hard to assess.

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Murmurs

Factors in genesis.—It is beyond the scope of this discussion to consider in detail the physical principles involved in the mechanism of murmur production. There are a few basic principles which, if understood, lead to a more thorough appreciation of the various clinical characteristics of murmurs.

Murmurs are caused by vibrations of cardiovascular structures due to turbulent blood flow. This may depend on several factors, such as: *(1)* velocity of blood flow; *(2)* pressure differences across orifices; and *(3)* anatomic abnormalities, such as deformity, incompetence or stenosis of a valve, and dilatation or constriction of a vessel.

In anemia, pregnancy, thyrotoxicosis, and the innocent functional murmur, turbulence from increased velocity of blood flow is responsible for the murmur which is heard. In anemia, low blood viscosity is a factor and favors murmur production.

When a murmur is caused by a high pressure difference across a small orifice leading to high blood velocity, it is usually high pitched (e.g., in aortic insufficiency). When there is a low pressure difference across a relatively large orifice and slow velocity of flow, there may be no murmur (e.g., in atrial septal defect), or a low-pitched murmur is produced (e.g., mitral diastolic rumble) (53).

Freely vibrating but nonobstructive structures, such as a ruptured papillary muscle or chorda tendinea, retroverted aortic cusp, or even the fine web of a Chiari network, may give rise to murmurs which may be musical (68). With sudden constriction or dilatation of a vessel or valve, there is a rapid change of velocity of blood flow which causes turbulence.

In many cases, the severity of a lesion cannot be estimated by the loudness of the murmur. Several other factors, such as timing, quality, pitch, or associated features, may be more important. Thus, a small ventricular septal defect may be associated with a loud murmur because the pressure difference between the right and left ventricle is so great that blood flows across the defect at high velocity. With defects so large that in effect there is a single ventricle, the pressures are equal and there is little or no murmur. In mitral stenosis and severe pulmonary hypertension, the cardiac output and flow across the mitral valve may be so reduced that no murmur is heard, and the opening snap and/or abnormally loud first sound may be the only clue to the presence of mitral valve stenosis. A lesion may form, due to repeated trauma, at the site at which a stream of blood under high velocity and pressure hits the endocardium, valve, or intima of a vessel (36, 99).

There is fibrosis, thickening, and roughness of the intima or endocardium at these sites. Vibrations which are caused when the jet stream hits these areas are thought to be responsible for the genesis of murmurs when there is a high-pressure gradient and a high-velocity jet flow through a narrow orifice. Such lesions are rare in cases of relatively slow blood flow across a large orifice (e.g., in mitral stenosis).

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functional murmurs are crescendo–decrescendo, and hence diamond shaped in the absence of aortic or pulmonary stenosis.

Pathologic systolic murmurs.—Although many anatomic and hemodynamic conditions cause systolic murmurs, excluding the innocent one, two basic types of murmurs are recorded phonocardiographically (53).

Stenosis of a semilunar valve, of the outflow tract of a ventricle, or of the supravalvular area produces a midsystolic ejection murmur (Plate 9). That is, following a brief silence after closure of the A–V valves there is a murmur which has a crescendo–decrescendo quality, ends before the second sound, and is usually diamond shaped when recorded. The ejection murmur must be related to valve closure events of the side of the heart from which it originates. The phonocardiogram in a case of pulmonary stenosis (Plate 7, *D*) is an example: the murmur started shortly after right ventricular ejection and ended before the pulmonary component of the second sound. It is usually diamond shaped, but of greater importance in the analysis is its relation to the heart sounds. The murmur may extend to and bury the aortic component of the second sound so that it is inaudible, and since the pulmonic component is often diminished in intensity and not heard the murmur may give the auscultatory illusion of being pansystolic. In such cases, the phonocardiogram is invaluable. The second pulmonic sound can be identified phonocardiographically in 85 per cent of the cases of pulmonary stenosis and indicates that one is dealing with a midsystolic ejection murmur (57). In tetralogy of Fallot, the murmur is sometimes softer because the flow through the overriding aorta offers less resistance than the stenotic pulmonary outflow tract and valve. In tetralogy, the second sound is single (aortic), loud, and occurs distinctly after the end of the murmur. Because of equal pressures in the right and left ventricles, there is little flow through the ventricular septal defect and the murmur of ventricular septal defect is usually absent. With ejection murmurs, the interval between the first sound and the onset of the murmur varies according to the time it takes for the ventricular pressure to rise above the pulmonary or aortic pressure (depending on which valve is stenosed). It is therefore related to the isometric contraction period of the involved side of the heart.

Ejection is rapid and under high pressure through a narrowed orifice, giving rise to a crescendo–decrescendo murmur. The murmur ceases after the ventricles begin to relax even though there is a negligible amount of forward flow through the valve, and therefore it ends before the closure of the appropriate semilunar valve.

Ejection murmurs may occur in the absence of anatomic stenosis.

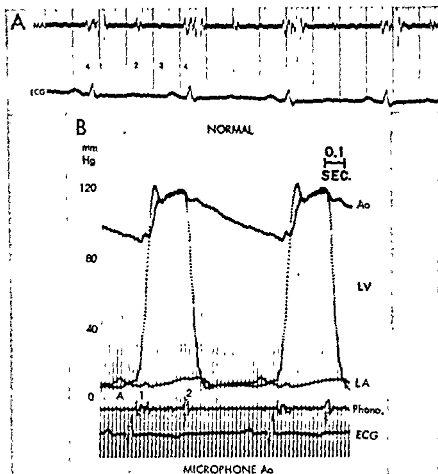


PLATE 1.—Normal heart sounds (79). A, the four components of the normal cardiac cycle; fourth (atrial) sound may be recorded, but is usually inaudible. B, phonocardiogram and aortic and left ventricular pressure curves in normal dog; microphone is in aorta. The two components of first sound correspond to crossing of ventricular pressure curve with left atrial and aortic pressure curves, i.e., mitral valve closure and aortic valve opening; latter is normally inaudible, but in this case is heard because microphone is just above aortic valve. Aortic second sound occurs when ventricular pressure falls below aortic at the time of aortic valve closure.

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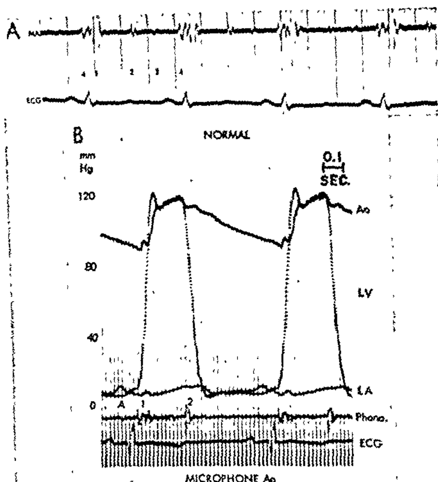


PLATE 1.—Normal heart sounds (79). A, the four components of the normal cardiac cycle; fourth (atrial) sound may be recorded, but is usually inaudible. B, phonocardiogram and aortic and left ventricular pressure curves in normal dog, microphone is in aorta. The two components of first sound correspond to crossing of ventricular pressure curve with left atrial and aortic pressure curves, i.e., mitral valve closure and aortic valve opening, latter is normally inaudible but in this case is heard because microphone is just above aortic valve. Aortic second sound occurs when ventricular pressure falls below aortic at the time of aortic valve closure.

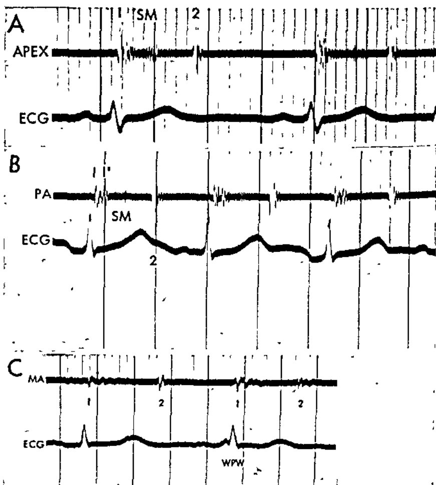


PLATE 2.—Functional murmurs. A, short systolic murmur at apex in subject without heart disease. B, pulmonary systolic murmur and normal splitting of first heart sound in patient with anemia, but without heart disease. C, intermittent *Wolff-Parkinson White syndrome; no difference in intensity of first sound in first* (normally conducted) and second (Wolff-Parkinson-White) beats

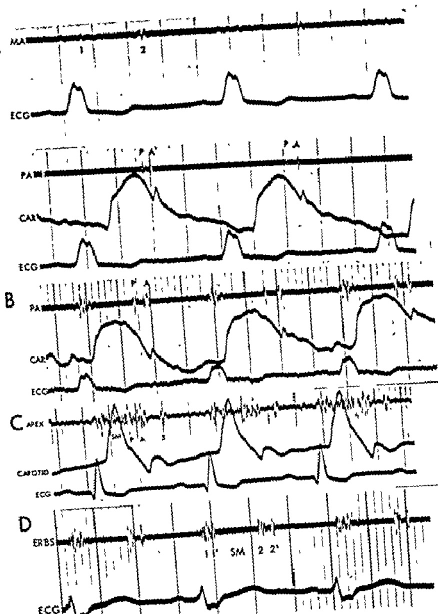


PLATE 5.—Splitting of heart sounds. A, rare example of delayed first sound in left bundle-branch block; note paradoxic splitting of second sound. B, usual, normal first sound and paradoxic splitting of second sound in left bundle branch block. C, paradoxic splitting of second sound in patent ductus arteriosus; prominent third sound. D, splitting of first and second sounds in right bundle-branch block.

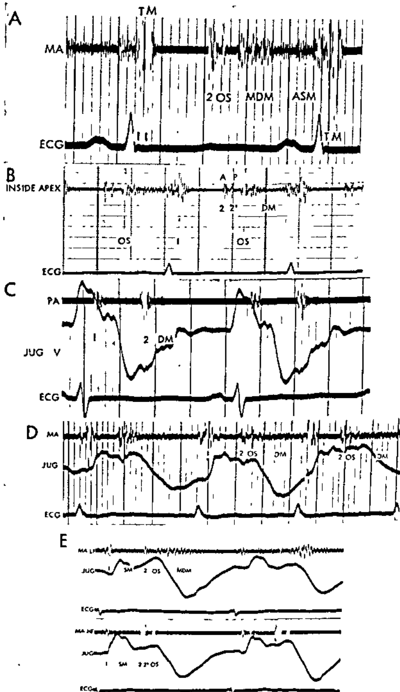


PLATE 4.—Legend on facing page

PLATE 4.—*Mitral stenosis. A, loud first sound; mitral closure probably followed tricuspid closure; silent gap after opening snap is followed by mid-diastolic murmur and atriosystolic (presystolic) murmur.* B, widely split second sound followed by opening snap, which is the loudest sound in cardiac cycle. C, pulmonary hypertension in mitral stenosis; loud second pulmonary sound and early decrescendo diastolic murmur (Graham Steell murmur), followed by short diastolic murmur, probably mitral in origin. D, variation in 2-OS interval in atrial fibrillation; in second cycle, which follows a long diastole, 2-OS interval is 0.08 second; third cycle follows shorter diastole and 2-OS interval is 0.06 second. E, low- and high-frequency phonocardiograms in combined mitral stenosis and insufficiency; first sound is not accentuated, pansystolic murmur, and an opening snap at peak of V wave *of jugular pulse; mid-diastolic murmur recorded only with low-frequency system.*

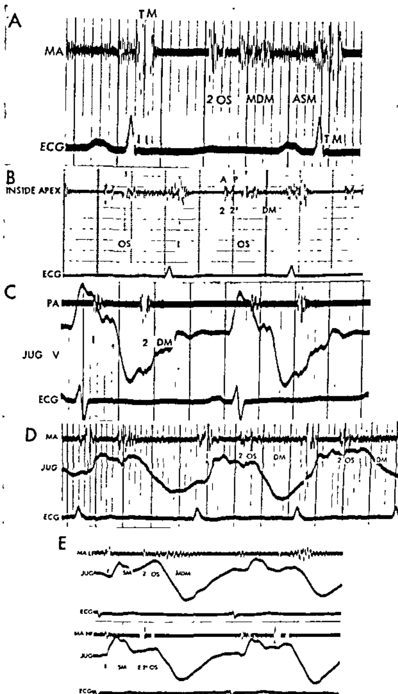


PLATE 4 —Legend on facing page

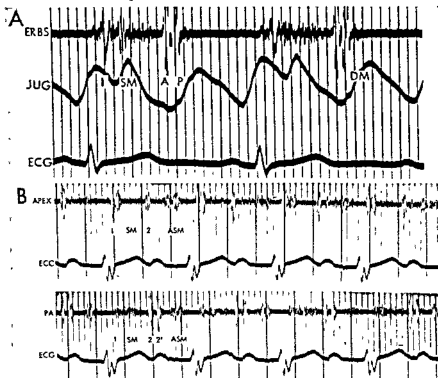


PLATE 6.—Atrial septal defect. **A**, ostium secundum defect; systolic ejection murmur and wide splitting of second sound (0 06 second). **B**, ostium primum defect; widely split second sound over pulmonary area but not at apex; prolonged P–R interval and an atriosystolic murmur (ASM).

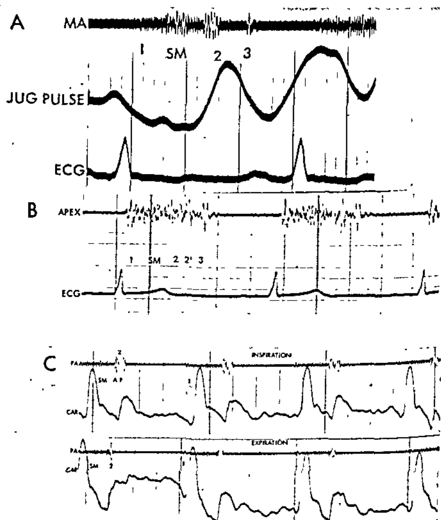


PLATE 5.—Mitral regurgitation. A, first sound diminished or absent; pansystolic murmur, and prominent third sound on descent of V wave of jugular pulse. B, late systolic crescendo murmur, split second sound, and prominent third sound. C, same case as in B; on inspiration, second sound in pulmonary area widely split (0.05 second), with expiration, splitting disappears, as in normal subjects, rapidly rising and falling carotid artery pulse, commonly found in mitral regurgitation.

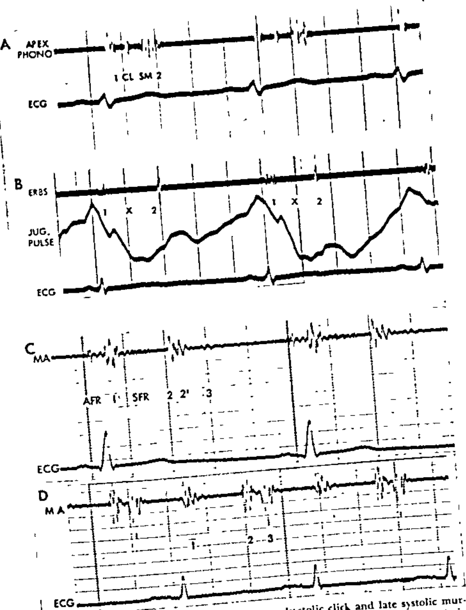


PLATE 8.—Systolic and diastolic sounds. A, midsystolic click and late systolic murmur in subject without heart disease. B, low pitched midsystolic sound (x) in another subject without heart disease. C, idiopathic pericarditis; presystolic (atrial) and systolic friction rub pericarditis, split second sound, and third sound. D, chronic constrictive pericarditis, loud early diastolic sound.

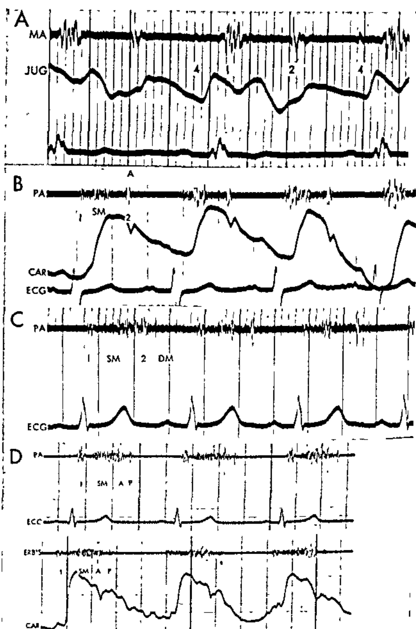


PLATE 7.—Pulmonary stenosis A, tetralogy of Fallot, single second sound at mitral area, due to aortic closure B, tetralogy of Fallot; ejection murmur ends before single (aortic) second sound C, same patient as in B after Blalock operation; note continuous murmur. D, normal aortic root; pulmonary component of second sound is diminished and delayed, systolic ejection murmur starts after first sound, continues up to and embraces aortic second sound, but ends before pulmonary closure

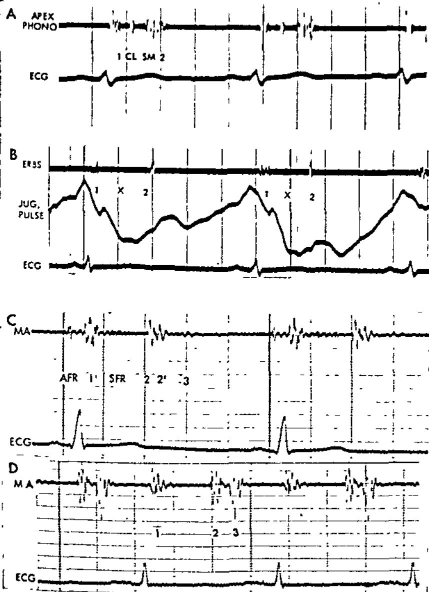


PLATE 8.—Systolic and diastolic sounds A, midsystolic click and late systolic murmur in subject without heart disease B, low-pitched midsystolic sound (x) in another subject without heart disease. C, idiopathic pericarditis; presystolic (atrial) and systolic friction rub pericarditis, split second sound, and third sound D, chronic constrictive pericarditis, loud early diastolic sound.

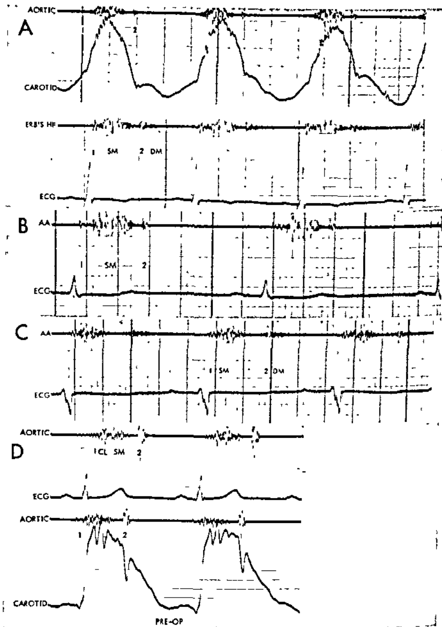


PLATE 9.—Aortic stenosis and insufficiency. **A**, aortic stenosis; ejection murmur, delay in rise of carotid artery pulse, and thrill on pulse; over Erb's area, high-pitched diastolic murmur, indicating aortic insufficiency. **B**, pure aortic stenosis, typical systolic ejection murmur. **C**, aortic regurgitation; decrescendo diastolic murmur; systolic ejection murmur caused not by aortic stenosis but by ejection of large volume of blood into dilated aorta. **D**, congenital aortic stenosis; aortic ejection click **(CL)** preceding systolic murmur.

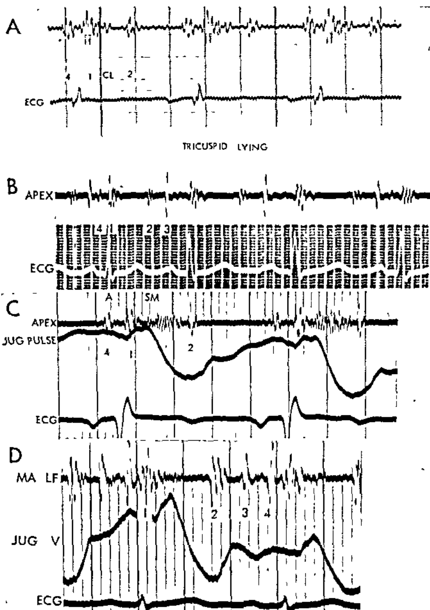


PLATE 10.—Triple and quadruple rhythms. A, right atrial myxoma; presystolic (atrial) gallop and systolic sound giving rise to quadruple rhythm. B, summation gallop, caused by almost coincident third and fourth (atrial) sounds C, pulmonary stenosis, right atrial gallop. D, acute rheumatic carditis; quadruple rhythm

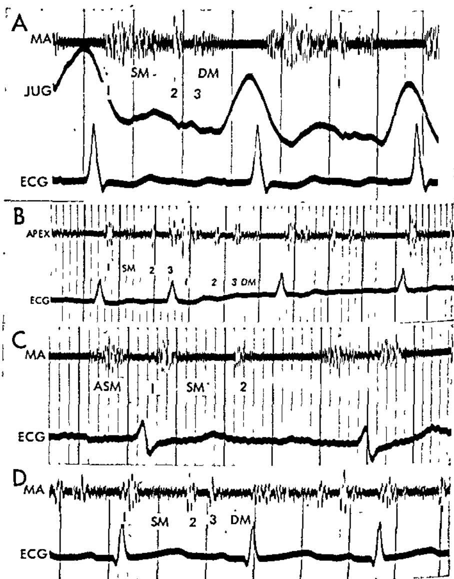


PLATE II.—Murmurs. A, fibroelastosis; pansystolic and mid-diastolic (Carey Coombs) murmurs. B, *rheumatic carditis with atrial fibrillation*; protodiastolic gallop followed by Carey Coombs mid-diastolic murmur; loudest first sound follows shortest diastole interval. C, rheumatic carditis with first degree heart block, diamond shaped ejection type of murmur, caused by atrial contraction (ASM). D, tachycardia, diastolic murmur following third sound is presystolic.

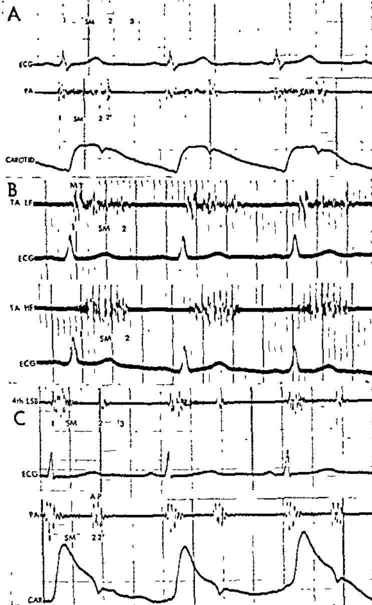


PLATE 12.—Ventricular septal defect A, pansystolic murmur, wide splitting of second sound, and prominent third sound B, low- and high-frequency (HF) records; diamond shaped, pansystolic murmur recorded by high frequency, should not be mistaken for murmur of aortic or pulmonary stenosis which is not pansystolic. C, systolic murmur ending before second sound in mild defect, could conceivably be a case of a muscular defect, which closes during systole and causes murmur to end before second sound

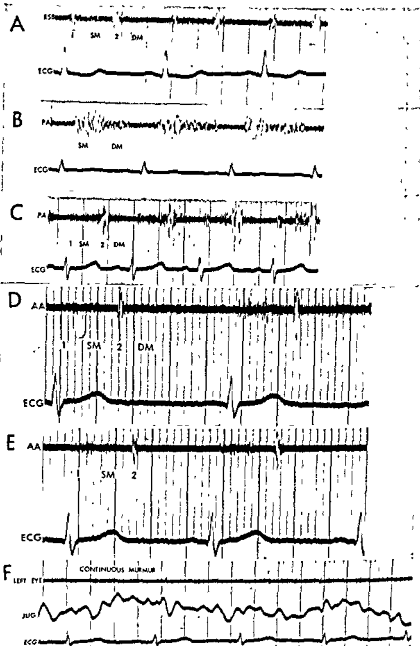


PLATE 13.—Continuous murmurs. A, *ruptured aneurysm of sinus of Valsalva;* in this case murmur is best heard along right sternal border. B, aortopulmonary septal defect. C, *patent ductus arteriosus, accentuation of continuous murmur near second sound.* D, continuous bruit due to venous hum. E, same case as in D; bruit *eliminated by jugular compression.* F, *aneurysm of left ophthalmic artery;* continuous murmur over left eye.

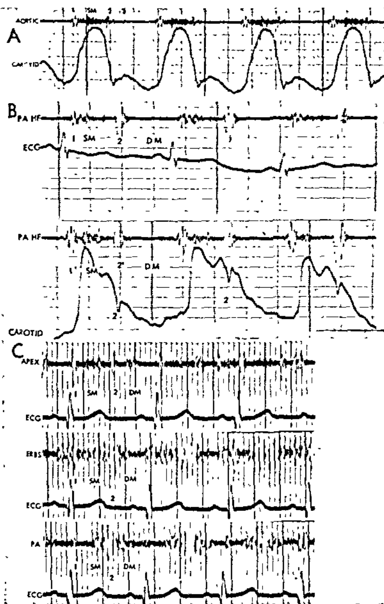


PLATE 14.—Patent ductus arteriosus A, systolic ejection murmur and slow rising carotid pulse simulating aortic stenosis in case with marked pulmonary hypertension. B, systolic ejection murmur and loud, narrowly split second sound in case with pulmonary hypertension; prolonged diastolic murmur ending just before first sound. C, loud, continuous murmur at pulmonary area and Erb's point in typical case, mid diastolic (Carey Coombs) murmur at apex due to increased flow through mitral valve.

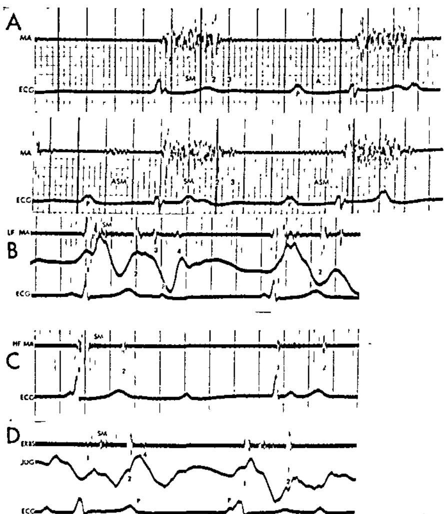


PLATE 15.—Complete heart block. A, atrial sound or atriosystolic murmur caused by each atrial contraction. B, prominent heart sound, atrial sound (4) occurs 0.12 second after onset of P wave. C, "bruit de canon" phenomenon, in first cycle, atrial contraction just precedes ventricular contraction and loud first sound is produced; ejection murmur is caused by large stroke volume. D, another case with ejection murmur and "bruit de canon" phenomenon.

In atrial septal defect, such a murmur is due to an abnormally large volume of flow through a normal valve orifice (relative stenosis). In complete heart block, stroke volume is increased and a typical ejection murmur may occur due to relative stenosis. In aortic regurgitation (Plate 9, C) a typical ejection murmur may occur in the absence of aortic stenosis. In fact, minimal regurgitation which increases stroke output increases the intensity of the murmur in valvular stenosis by increasing forward flow during systole (53).

PANSYSTOLIC MURMURS (Plate 12).—The murmurs of mitral regurgitation and of ventricular septal defect with left-to-right shunt are the prototype of murmurs which occupy the entire systolic interval because a pressure difference exists throughout systole. Hence they are referred to as pansystolic or holosystolic. They are caused by blood flow from a chamber of higher pressure to one of lower pressure. They are pansystolic. In uncomplicated ventricular septal defect with left-to-right shunt, the pressure in the left ventricle exceeds that of the right ventricle throughout systole and hence blood flow is continuous during that time. In mitral or tricuspid regurgitation, backward flow continues through systole because ventricular pressure exceeds atrial pressure throughout this interval. In mitral regurgitation, the murmur continues slightly past the aortic second sound because ventricular pressure exceeds atrial pressure even after the aortic semilunar valve closes.

The shape of pansystolic murmurs is of little importance. They may be diamond shaped or have an early or late systolic accentuation. It is their pansystolic character which is most important in their evaluation.

DIASTOLIC MURMURS.—Physiologically, two types of diastolic murmurs occur: those due to stenosis of A–V valves, and those due to regurgitation as a result of incompetent semilunar valves (53). The character of these murmurs is such that differentiation is possible on clinical grounds alone.

The prototype of ventricular filling murmurs is the diastolic rumble of mitral stenosis (Plate 4). A normal volume of blood flows across a narrowed orifice under low pressure, and consequently the murmur is of low frequency when recorded and rumbling is heard on auscultation.

Aortic or pulmonary regurgitation murmurs are distinctly different from ventricular filling murmurs (Plate 9, C). In aortic regurgitation, the pressure differential across the aortic valve in diastole virtually amounts to the diastolic pressure, since the ventricular pressure is essentially zero during this phase. Thus, with minimal aortic incom-

petence, there is a high pressure difference (approximately 70 mm. Hg) across a small orifice and a high-pitched murmur is produced. When the lesion becomes significant and the aortic diastolic pressure is low, the murmur may be louder and more readily perceived, but it is usually of lower pitch. The murmur begins immediately after closure of the semilunar valve and continues throughout diastole because there is a persistent pressure difference between the aorta and left ventricle. Not infrequently, such murmurs are difficult to hear and even more difficult to record because they are of high pitch and low intensity. This is the best proof that phonocardiography cannot at present replace auscultation.

CONTINUOUS MURMURS (Plate 13).—Several conditions are associated with a continuous murmur: patent ductus arteriosus, aortopulmonary septal defect, arteriovenous fistula, dilated bronchial arteries (as in pulmonary atresia), rupture of the sinus of Valsalva into the right ventricle or pulmonary artery, and even a venous hum may evoke continuous murmurs. Occasionally, in ventricular septal defect with aortic insufficiency, the systolic and diastolic murmurs sound as though they were continuous, and lead to an erroneous diagnosis of patent ductus arteriosus.

Neil and Mounsey (87) have described the clinical and phonocardiographic characteristics of the continuous murmur of patent ductus arteriosus. The murmur is continuous unless there is pulmonary hypertension, in which case the murmur may be only systolic, or systolic and diastolic (Plate 14, *A* and *B*). Phonocardiographically, the murmur may end before and begin just after the first sound and rise to a crescendo in late systole. No exact explanation for the accentuation of the murmur in late systole near the second sound has been found, as the greatest difference in pressure between the aorta and pulmonary artery occurs in midsystole, but it may be due to a delay in transmission to the ductus. Because left-sided output is increased in patent ductus arteriosus, left ventricular ejection is prolonged, and aortic valve closure (paradoxic splitting of the second sound) may be delayed (42) (Plate 3, *C*). In conditions other than patent ductus arteriosus, the continuous murmur may be accentuated earlier or later and may be best heard in areas other than the pulmonary, but the clinical differentiation may be difficult (43). In aortopulmonary septal defect (Plate 13, *B*), the timing and location of the murmur may be identical. Other less common causes of continuous murmurs include total anomalous venous return (68), multiple congenital stenosis of pulmonary arteries (38), coarctation of the aorta, and any systolic plus early diastolic murmurs, such as in aortic stenosis and insufficiency.

The Potts and Blalock operations for tetralogy of Fallot are designed to increase pulmonary flow by the creation of an A–V fistula. *A continuous murmur following the operation indicates a functioning* anastomosis but gives no clue about the adequacy of the shunt. Disappearance of the continuous murmur usually indicates thrombosis at the anastomotic site.

The venous hum is louder on inspiration and in early diastole due to increased flow to the heart when intrathoracic pressure falls. *Occluding the jugular vein with the finger eliminates this continuous* bruit. The so-called mammary souffle of pregnancy may be mistaken for a continuous murmur of cardiovascular origin. It is probably arterial in origin, caused by increased flow to the breasts during the later months of pregnancy. Pressure on the stethoscope will eliminate this murmur, which sounds more superficial than that of a patent ductus arteriosus (101).

PHONOCARDIOGRAPHIC FEATURES OF SOME COMMON CARDIOVASCULAR DISORDERS

Mitral Stenosis and Regurgitation

Stenosis (Plate 4).—Awareness of the various sounds and murmurs which may be present is more important in mitral stenosis than in any other valvular lesion. It is not only the commonest valvular malformation encountered in adults but is also one of the heart lesions most amenable to surgical correction. Auscultation and phonocardiography give information in regard to the anatomy, physiology, and prognosis in this lesion.

The first sound is sharply accentuated, and this may be the earliest sign of the disease (59). The exact cause for the accentuation is not known, but it is certainly related to the valves or the chordae tendinae rather than to the myocardium. The first sound is delayed (prolonged Q-1 interval), sometimes for as long as 0.12 second (normal, 0.02–0.06 second). This, however, can be ascertained only by the phonocardiograph. The delay *is roughly proportional to the elevation of the left atrial pressure, and the mitral component of the first heart sound may follow the* tricuspid component rather than precede it.

In patients with atrial fibrillation, the intensity of the first sound varies inversely with the length of the preceding diastole (92), although we have found some exceptions. The delay of the first sound also varies inversely with the length of the preceding diastole (76).

The second sound may be reduplicated, with accentuation of the

pulmonary component. The splitting is usually narrow; rarely, is it wide. In pulmonary hypertension, the pulmonary component is accentuated, but, contrary to common belief, the split is narrow. It must not be forgotten that the opening snap may be well heard in the pulmonary area and be mistaken for a widely split second sound (122).

The opening snap has already been discussed, but it is worth emphasizing that this is one of the most characteristic findings in mitral stenosis (74, 80) (Plate 4). Not only may it be the first auscultatory phenomenon and precede the appearance of the diastolic murmur, but the absence of the snap should make the clinical diagnosis of mitral stenosis at least doubtful. However, the opening snap of mitral stenosis may be absent when there is heavy calcification, aortic insufficiency (124), or predominant mitral regurgitation.

The 2-OS interval varies inversely with the left atrial pressures: the higher the left atrial pressure, the earlier the mitral valve opens and the shorter is the 2-OS interval. In atrial fibrillation, the 2-OS interval varies proportionately to the length of the preceding diastole (Plate 4, *D*).

The diastolic murmur is rumbling in character and may be confined to a small area of the apex or midaxillary region, especially if the apex is displaced posteriorly by an enlarged right ventricle (88). The murmur begins immediately or shortly after the opening snap. The length of the murmur is the best guide to the severity of the mitral stenosis (124). If confined to mid-diastole, the filling gradient has been rapidly equalized and signifies a small or modest rise in left atrial pressure. If, however, the murmur is long and continues up to the first sound, there is a persistent gradient throughout diastole and signifies severe stenosis. With heavy calcification, the diastolic murmur may become higher pitched and even musical. However, it never starts with the second sound and even in the absence of an opening snap its occurrence in mid-diastole differentiates it from the diastolic murmur of aortic regurgitation.

The presystolic murmur is due to atrial contraction just before ventricular systole, and has been termed the atrial systolic murmur. As would be expected, it disappears after a change of rhythm from sinus to atrial fibrillation (Plate 4, *E*).

The diastolic murmur may be absent in severe mitral stenosis with primary hypertension and a reduced cardiac output; this has been explained on the basis of marked reduction in flow across the mitral valve (66). Rotation of the heart or pulmonary disease may also be a factor when the murmur is absent. In such cases, a loud M_1 and an opening snap may provide the only bit of phonocardiographic or auscultatory evidence of mitral stenosis.

In many cases, there is an early apical systolic murmur which is not caused by mitral regurgitation (82). The murmur is not pansystolic, and at operation there is no regurgitant jet. The cause for this murmur is in doubt. Minimal mitral regurgitation or tricuspid regurgitation may be responsible, or basal systolic murmurs may be transmitted to the apex and interpreted as mitral in origin.

On the phonocardiogram, the diastolic murmur is of low frequency and follows the opening snap. We have often recorded it using the low-frequency (stethoscopic) system, and at the same time have been unable to register the murmur using the high-frequency (logarithmic) system (Plate 4, *E*). This is in accord with the common clinical experience that the murmur is inaudible when the diaphragm of the stethoscope is used but is readily heard when the bell is applied lightly to the apex.

The left lateral position often brings out the murmur. This position brings the apex closer to the chest wall so that the murmur is better heard, although the effort involved in turning may accentuate the murmur. Moderate exercise, by increasing cardiac output, also may bring out the diastolic murmur; if the rate is too fast, however, auscultation is defeated and becomes confusing.

Tumors of the left atrium (usually a myxoma) or a ball-valve thrombus can produce all of the auscultatory signs of mitral stenosis, including the opening snap (58). Often, the only clue to the presence of a pedunculated tumor is a disappearance of the diastolic rumble when the position is changed from the upright to the supine (9). In true valvular mitral stenosis, the converse is more commonly observed, and the murmur is better heard in the supine position.

In older patients with tight mitral stenosis and calcified leaflets, there may be no murmur, either in systole or diastole, no snap, and no accentuation of the first sound. The late first sound and the absence of the gallop, which would be expected in left heart failure of equal severity, serve to awaken suspicion of the presence of an operable lesion.

Pure regurgitation (Plate 5).—The intensity of the first sound is normal or diminished, and occasionally is extremely faint or absent in pure mitral regurgitation. It is never accentuated (14, 122). The split of the second sound may be wider than normal; the sound is best heard other than at the apex. Since marked pulmonary hypertension is uncommon, the pulmonary component of the second sound is not conspicuously accentuated and pulmonary incompetence is rare except in the presence of heart failure. An opening snap is rarely, if ever, associated with pure regurgitation; its presence points to concomitant mitral stenosis (14, 122).

A prominent apical third sound is a frequent finding (14). It is caused by abnormally rapid left ventricular filling, since a larger stroke volume is necessary to compensate for the amount of blood regurgitating into the left atrium. When there is torrential filling, a mid-diastolic rumble (Carey Coombs murmur) may be heard; this must not be considered as evidence of mitral stenosis.

The murmur is pansystolic because ventricular pressure exceeds atrial even after aortic valve closure (14, 53). It is maximal at the apex in expiration and radiates toward the axilla and left scapula. It is rarely louder than grade 2 at the base (14). The quality of the murmur varies considerably, ranging from harsh to soft, but it is generally of high pitch. With valve calcification or rupture of a papillary muscle, a musical murmur may be present (98). Late systolic accentuation of the murmur occurs in some patients with mild to moderately incompetent valves (14, 53).

Rupture of one or more of the papillary muscles and calcification of the annulus fibrosus commonly cause harsh or musical murmurs. A loud murmur as well as a thrill may then be present over the aortic area or carotid arteries (36).

Graphically, the murmur may have a crescendo ranging from early to late, or it may be of even amplitude throughout. However, the murmur always begins with the first sound and extends to the aortic component of the second sound. Occasionally, it extends even beyond the pulmonary component, which accounts for the early diastolic murmur in these cases (14); when this is present, however, aortic or pulmonary regurgitation cannot be ruled out with certainty. The Q-1 interval is usually not prolonged in pure mitral regurgitation.

Combined stenosis and regurgitation.—One of the most difficult problems in clinical cardiology is the determination of the dominant lesion in cases of combined mitral stenosis and insufficiency. This is becoming increasingly important since newer technics in surgery now allow correction of mitral regurgitation. Elaborate diagnostic procedures designed to differentiate dominant stenosis from insufficiency and to detect minimal degrees of stenosis and insufficiency have been proposed. However, many of these procedures are time consuming, costly, and associated with a significant morbidity. In addition, the results have not been uniformly reliable.

At the present time, on the basis of the experience gained in mitral surgery over the past decade, the dominant lesion can be predicted with a high degree of accuracy by auscultation alone. In general, in a patient with a combined mitral lesion, the following features indicate predominant stenosis: *(1)* a loud first sound; *(2)* an opening snap; *(3)*

a long diastolic murmur; and *(4)* a systolic murmur grade 2 or less (on a scale of 6). Mitral regurgitation is the dominant lesion if: *(1)* the first sound is soft; *(2)* there is an apical pansystolic murmur grade 3 or louder; *(3)* there is a third sound rather than an opening snap; and *(4)* the diastolic murmur is of brief duration.

Patients with a grade 3 or louder pansystolic murmur associated with the pathognomonic signs of mitral stenosis usually are found to have predominant stenosis at operation. However, the insufficiency is so severe that commissurotomy is generally unsuccessful. Patients with the signs of mitral insufficiency associated with a diastolic rumble are usually found to have mainly insufficient valves at operation.

Heavy calcification of the mitral valve in pure mitral stenosis may result in an absence of the loud first sound, and of an opening snap, and even of a loss of the diastolic murmur. However, even when such cases are recognized clinically, the mitral valves are so severely damaged that surgery can offer little help and is usually contraindicated.

Aortic Stenosis and Regurgitation (Plate 9)

Stenosis.—The intensity of the first sound is ordinarily normal, but with cardiac failure the intensity of the heart sounds and of the murmur may be diminished. An early systolic ejection sound (Plate 9, *D*), presumably caused by sudden distention of the aorta, occurs in some two-thirds of the patients with mild aortic stenosis; in severe stenosis, it is less common (123).

The second aortic sound may be normal, diminished, or rarely absent. Because left ventricular ejection is prolonged, the aortic second sound is often delayed and paradoxic splitting of the second sound then occurs (42, 47, 49).

Several variations of the ejection murmur of aortic stenosis may occur. Although in all cases there is a midsystolic murmur, on auscultation its intensity, its quality, or the area in which the murmur is best heard may vary. Typically, there is a high-pitched but rough murmur starting after the first sound and ending before the aortic component *of the second sound. Since the second sound may be of decreased in*tensity or inaudible, and the murmur may then seem to be pansystolic, a phonocardiogram is distinctly helpful.

The murmur is usually best heard in the aortic area, but is occasionally maximal at the apex (3) or in the neck over the carotid arteries (6). In these cases, the diagnosis can still be made with assurance on clinical grounds alone because of the timing, which serves to differentiate it from other murmurs. The murmur may be musical, harsh,

and occasionally is "sea gull" in quality, and tends to radiate toward the neck vessels.

A thrill is present in approximately one-half of the cases and may be felt at the apex or over the carotid arteries or jugular notch, especially if the murmur is maximal over these areas (123).

Graphically, there is a high-frequency crescendo–decrescendo murmur (hence diamond shaped) which starts after a brief pause following the first heart sound and ends before the aortic second sound, which may be delayed. It must be remembered that the murmur should be related to events occurring in the left side of the heart, and that the murmur may appear to be almost pansystolic if the aortic component is delayed, so that the murmur extends to and even beyond the preceding pulmonary second sound (49).

Attempts have been made to differentiate subaortic stenosis from valvular aortic stenosis, and innocent ejection murmurs simulating aortic stenosis from organic murmurs, solely on the basis of the phonocardiographic characteristic of the second sound (16) or whether there is an early or late diamond-shaped murmur (1). In our opinion, such a differentiation cannot be made with assurance on clinical grounds alone. Even acquired muscular hypertrophy of the left ventricular outflow tract secondary to systemic hypertension has been reported to be associated with the typical auscultatory and hemodynamic features of valvular aortic stenosis (15).

Finally, a high-pitched, early, blowing aortic diastolic murmur in severe aortic stenosis does not necessarily imply aortic incompetence of hemodynamic significance. It is merely an auscultatory sign reflecting failure of the aortic valves to close completely during diastole as a result of malformation, calcification, or severe fibrosis of the valve (Plate 9, *A*).

Regurgitation (Plate 9, *C*).—There is nothing characteristic about the first sound; it may be diminished, normal, or rarely accentuated. Auscultatory features may be confusing because of the occasional presence of an aortic ejection click which, being louder than the first sound, is often mistaken for it. The graphic features of the first sound may be difficult to define. We have observed variations in its intensity, but the association of other valve lesions, such as mitral stenosis or mitral insufficiency, which may alter the intensity of the first sound, makes its evaluation difficult. It is also difficult and apparently of little value to evaluate the Q-1 interval.

The second aortic sound is frequently accentuated and of a ringing, banging, or tambour quality. This is more frequently observed in luetic aortic regurgitation, but it occurs in the rheumatic form as well.

The pulmonary second sound is normal or accentuated. A third sound (protodiastolic gallop) is frequently observed. With coexisting mitral stenosis, the opening snap is delayed (102) or absent (124). There may be an early or midsystolic ejection click (8).

An aortic systolic ejection murmur is invariably present. Of itself, it does not indicate aortic stenosis, and in fact the murmur may be very loud and associated with a thrill (52). This is caused by the increased stroke volume through a normal-sized orifice (relative stenosis).

The diastolic murmur varies considerably, due to poorly understood factors. In quality, it is usually high pitched, and blowing, puffing, or musical; rarely is it harsh. Retroversion of an aortic cusp produces a buzzing or musical murmur which is more likely to be associated with a thrill. The aortic diastolic murmur is heard best at the aortic area or Erb's point. It may be equally loud at the apex and its pitch may become lower. Rarely, it is maximal or heard solely in the left axilla (Cole-Cecil murmur) (23). Occasionally, the murmur is maximal along the right sternal border. This is especially true if the regurgitation is caused by rupture of a sinus of Valsalva into the right atrium or ventricle (Plate 13, *A*). However, it is erroneous to assume that the cause of the aortic regurgitation can be related to the area over which the diastolic murmur is loudest.

Graphically, the diastolic murmur begins with or very shortly after the aortic component of the second sound, and is decrescendo. In hemodynamically significant lesions, the murmur is pandiastolic, but often ends before the first sound. Due to its high-frequency characteristics, the murmur is best recorded with a stiff diaphragm with the high-frequency system.

The Austin Flint murmur has been the subject of many reports, most of them speculating on the mechanism of murmur production (30). Although Flint described it as a presystolic blubbering murmur (39), many cardiologists consider early, mid-, or late diastolic rumbles caused by aortic regurgitation as examples of the so-called Austin Flint murmur (102). Of greater importance is its differentiation from the diastolic rumble of mitral stenosis. This is at times difficult, especially if one relies solely on the quality of the murmur. The accessory auscultatory and phonocardiographic features serve to differentiate the two. Thus, in aortic regurgitation M_1 is usually not loud or delayed; there *is no opening snap; more likely a third heart sound is present*; and, most important, graphically the diastolic murmur usually begins with the aortic second sound.

The graphic characteristics of the murmur change only slightly after the Hufnagel operation despite objective signs of improvement. Some-

times the intensity is decreased. The clicking sound is best heard in, and recorded from, the left axilla or posteriorly.

Pulmonary regurgitation must be differentiated from aortic regurgitation. At times this may be difficult. Ordinarily, in pulmonary regurgitation the murmur radiates inferiorly along the left sternal border toward the xiphoid process, while the aortic diastolic murmur, though often best heard over Erb's point, radiates to the apex. The phonocardiogram is extremely valuable in these cases. Whereas in aortic regurgitation a loud A_2 is observed, in pulmonary regurgitation a loud P_2 would be expected. The peripheral signs of aortic regurgitation—a water-hammer pulse, Traube's sign (pistol shot) and *Duroziez's sign*—are helpful when present. When the carotid pulse is recorded simultaneously with the heart sounds, a rapid rise, rapid fall, and low dicrotic notch is characteristically observed in pure aortic regurgitation.

Tricuspid Valve: Stenosis and Regurgitation

Stenosis.—Organic tricuspid stenosis rarely occurs as an isolated lesion, and is invariably associated with mitral stenosis. The exact incidence is not known, but can be as high as 15 per cent (2) in patients with mitral stenosis. In Wood's (122) series of 300 consecutive cases of mitral stenosis, however, it was only 3 per cent.

The first heart sound may be accentuated, as in mitral stenosis (40). On the other hand, its intensity may be normal or even diminished (68). A presystolic or diastolic rumbling murmur accentuated on inspiration and decreasing in intensity on expiration is invariably present (95). It is maximal over the tricuspid area, but when the right ventricle is enlarged it may be louder at the apex and considered as mitral in origin. The murmur is at times extremely loud due to the superficial position of the tricuspid valve, and is more often associated with a thrill than is the murmur of mitral stenosis. Although the murmur is usually of rumbling quality it has been described as being high pitched, and "sea gull" in quality (21).

The tricuspid opening snap (21, 48) is usually later than the mitral snap, although it should be timed with the later pulmonary component rather than the earlier aortic second sound. This is due to the lower mean pressures observed in the right atrium in tricuspid stenosis as compared with left atrial pressures in mitral stenosis. In atrial fibrillation, the tricuspid 2-OS interval varies proportionately with the length of the preceding diastole (48). On inspiration, the tricuspid 2-OS interval shortens, due to a fall in the right ventricular pressure and subsequent greater filling gradient.

Right atrial myxomas can simulate the auscultatory features of tricuspid stenosis. Relative tricuspid stenosis causing a mid-diastolic rumble has been observed in cases of primary pulmonary hypertension and atrial septal defect, and a right-sided Austin Flint murmur in patients with pulmonary regurgitation (68).

Although it is not our purpose to describe here hemodynamic phenomena except as a physiologic approach to phonocardiography, an obvious advantage of phonocardiography is the precise timing of murmurs with venous, carotid, or hepatic pulsations. In cases of tricuspid stenosis with sinus rhythm, giant A waves of the jugular pulse and presystolic hepatic pulsations are characteristic features.

REGURGITATION.—As with mitral regurgitation, the murmur caused by tricuspid regurgitation is pansystolic. It is usually best heard just to the left or right edge of the lower sternum, but may be as loud or even louder at the apex, and when associated with mitral stenosis resort to surgery may be decided against because the murmur is erroneously interpreted as indicating significant mitral regurgitation (100). An increased intensity of the murmur on inspiration is a helpful sign (94), and if the venous pulse is typical and hepatic pulsations are present the diagnosis may be readily apparent. Often, however, it is difficult to establish the presence of tricuspid regurgitation on clinical grounds alone.

Graphically, early accentuation of the pansystolic murmur (83) is commonly observed but is not pathognomonic. Functional tricuspid regurgitation can occur in heart failure from any cause, and we have seen all the classic signs of this condition disappear with successful treatment of cardiac failure secondary to hypertensive heart disease.

PULMONARY STENOSIS (Plate 7)

Much the same can be said for the findings in pulmonary stenosis as for aortic stenosis, but they must be related to events occurring in the right side of the heart.

The intensity of the first sound is normal. The second sound is widely split and the pulmonary component is delayed proportionately to the severity of the stenosis (57). The second pulmonary sound is often decreased in intensity, and erroneously has been considered to be frequently absent. Phonocardiographic studies have shown that it is present in 85 per cent of the cases, and it usually can be heard if one listens carefully. The splitting of the second sound can be as wide as 0.14 second in very severe stenosis (57).

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times the intensity is decreased. The clicking sound is best heard in, and recorded from, the left axilla or posteriorly.

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age, this early systolic ejection click is heard 0.14 second after the onset of the QRS complex of the ECG, and, when timed with simultaneous pulmonary artery pressure curves, occurs 0.03 second after the rise in the right ventricular pressure curve and hence is related to early ejection.

There is a high-pitched, harsh, crescendo-decrescendo murmur maximal in the pulmonary area and frequently accompanied by a thrill. The murmur is midsystolic and usually diamond shaped on the phonocardiogram. It may extend beyond the earlier aortic component of the second sound. A diastolic murmur is rarely present unless valvulotomy has been performed, in which case an early diastolic murmur is common but is probably of no physiologic significance.

These features are similar in valvular or subvalvular stenosis, but are different if there is an overriding aorta (tetralogy of Fallot).

Atrial Septal Defect (Plate 6)

The first sound may be normal or increased in intensity. When increased, high rates of pulmonary flow are present (54). Splitting of the first sound is not conspicuous unless there is complete right bundle-branch block, in which case splitting is wide (11, 50). The mitral valve closes first and it is the tricuspid closure that is delayed. Often there is an early pulmonary systolic ejection sound, best heard over the pulmonary area.

The second sound is conspicuously split even in the expiratory phase of continuous respiration (71) (Plate 6). Unlike the normal, the width of its splitting is not significantly affected by inspiration (4, 54). There is a normal sequence of semilunar valve closure, i.e., aortic valve before pulmonary. The delay of pulmonic valve closure is caused by a prolonged right ventricular ejection period due to an increased stroke volume. In the presence of pulmonary hypertension, the splitting may be narrow or absent (54). Usually, the pulmonary component is normally loud, although the wide splitting gives an illusion that the pulmonary component is accentuated. With pulmonary hypertension, P_2 is accentuated; with associated pulmonary stenosis (valvular or hypertrophy of the crista supraventricularis), P_2 is decreased. A high-pitched, snapping diastolic sound occasionally occurs 0.03 to 0.12 second after the pulmonic valve closure and may represent a tricuspid opening snap (54). Following surgical correction of the atrial septal defect, the splitting may disappear (10).

The systolic murmur is usually best heard at the pulmonary area,

but occasionally is loudest over the third or fourth left intercostal space. The murmur is moderately loud (grade 2 to 4 on a scale of 6), but occasionally is very soft or very loud. It is high pitched, soft, or blowing rather than harsh. When the murmur is accompanied by a thrill, pulmonary stenosis should be considered. In ostium primum defects, a cleft in the mitral valve causes regurgitation with a distinctly separate, apical pansystolic murmur radiating to the axilla and left scapula.

The pulmonary systolic murmur is caused by ejection and hence begins after the first sound and ends distinctly before the pulmonary second sound. It is louder, harsher, and slightly more prolonged in the presence of pulmonary stenosis.

Diastolic murmurs are of two types (Plate 6, *B*): *(1)* An early, decrescendo, blowing murmur along the left sternal border represents pulmonary regurgitation and is associated with hypertension in the pulmonary circulation (4). *(2)* A short mid-diastolic murmur over the tricuspid area is more common; it occurs 0.02 to 0.04 second after the peak of the V wave of the right atrial pressure curve and hence is probably caused by increased flow through a normal tricuspid valve (84). A right atriosystolic murmur may occur with prolongation of the P–R interval (Plate 7, *B*). This is more commonly observed in cases of ostium primum defects.

Lutembacher's syndrome (atrial septal defect with mitral stenosis) is rare (85). An apical diastolic murmur is usually of tricuspid origin; it may be misinterpreted and thought to be due to mitral stenosis. In bona fide cases, there is an apical diastolic rumble, but often no opening snap is present.

VENTRICULAR SEPTAL DEFECT (Plate 12)

This defect may occur as an isolated lesion (pure ventricular septal defect) or in combination with other lesions: with an overriding aorta and pulmonary stenosis (tetralogy of Fallot), and with aortic regurgitation. Most defects are located in the membranous septum, but muscular defects produce similar features. Physiologically, the pulmonary vascular resistance is the most important factor (125). Awareness of the variations in the phonocardiographic and auscultatory findings is important, because a great deal of useful information may be obtained merely from auscultation.

Auscultatory evaluation of the first and second sounds is difficult because the pansystolic murmur embraces both sounds. The phono-

cardiogram, however, allows precise evaluation: The first sound is normal or loud. The second sound may be normally or moderately split, but wide splitting (0.05 second) is not uncommon (7). Hypertension in the pulmonary circulation narrows the splitting and accentuates the pulmonary component. In pulmonary stenosis, the second pulmonic component is diminished. In tetralogy of Fallot, the pressures in the two ventricles are equal (hence there is negligible flow through the defect) and the murmur is that of pulmonary stenosis. A pulmonary ejection click is less frequently observed in ventricular than in atrial septal defects.

The characteristic murmur is pansystolic, high pitched, and harsh (Plate 12). It is usually loudest at the left fourth sternal border and is accompanied by a thrill. Graphically, it is often crescendo–decrescendo (diamond shaped), but should not be confused with the midsystolic ejection murmur of aortic stenosis, because it is pansystolic and extends to the aortic second sound (126).

A loud systolic murmur has been observed in several patients, and was at first thought to be representative of VSD. At catheterization, however, an oxygen step-up in the right ventricle could not be confirmed. Graphically, the murmur was noted as just short of being pansystolic, but commenced with the first heart sound (Plate 12, *C*). Leatham (53) suggested that contraction of the muscular septum could close a defect so small that a left-to-right shunt cannot be detected; in 1 patient this was proved by angiocardiography.

A prominent third heart sound with or without a Carey Coombs type of mid-diastolic murmur may be recorded. This is caused by torrential blood flow across the mitral valve (126). A pulmonary diastolic murmur from regurgitation occurs when there is pulmonary hypertension. With high pulmonary pressures due to increased pulmonary vascular resistance (Eisenmenger's syndrome), flow through the defect decreases and becomes bidirectional or even predominantly right to left. The loudness of the harsh systolic murmur decreases markedly. When the defect is huge so that essentially there is only a single ventricle, the murmur may be insignificant or absent.

In aortic regurgitation, an aortic or apical pandiastolic murmur is present. Combined with the systolic murmur, a continuous murmur may then be present and simulate patent ductus arteriosus. In both cases, there is a wide pulse pressure and the peripheral signs of aortic regurgitation. Graphically, the continuous murmur of patent ductus is maximal near the second sound making identification of its individual components difficult, whereas in VSD with aortic regurgitation the second sound can be readily identified as a rule.

Coarctation of the Aorta

The phonocardiographic and auscultatory signs of coarctation of the aorta may be caused by the coarctation itself, by associated anomalies such as bicuspid aortic valve stenosis, or by collateral vessels. To understand the marked difference in the clinical findings, it is essential that the anatomic variations in the site of the coarctation should be borne in mind. Thus, the coarctation may be single and in the usual site (just distal to the left subclavian artery), or it may be abdominal in location, or the patient may have several coarctations. In the so-called infantile type, the entire aortic isthmus is markedly hypoplastic, or there may be complete occlusion of the aorta.

An early aortic ejection click may be caused by coexisting aortic stenosis or be due to increased aortic resistance from the coarctation alone.

The murmur produced at the site of the coarctation theoretically should be loudest over the left interscapular area. This is true in most cases; however, occasionally the murmur is equally loud or louder over the pulmonary area or precordium. In such cases, it is difficult to exclude aortic stenosis; however, if caused only by flow through the coarctation, the murmur is delayed because of its origin at a distal site.

Generally, the murmur is systolic, but many variations may occur (22, 117). It may extend into early diastole because of a delay in transmission, or there may be a continuous murmur (posteriorly) because of continuous flow through collateral vessels. Graphically, the murmur is of high frequency with an early, late, or no crescendo, and extends to the second sound or into diastole. In addition, there may be all of the classic phonocardiographic signs of aortic stenosis when this lesion coexists. In such cases, the second aortic sound is diminished, but in the absence of aortic stenosis there is ordinarily an accentuated aortic closure sound.

Aortic regurgitation may coexist, but more commonly there is a high-pitched, early diastolic murmur, indicating a deformed or bicuspid valve without hemodynamically significant aortic incompetence (20, 124).

Tetralogy of Fallot (Plate 7, *A* and *B*)

This lesion has two defects which ordinarily cause murmurs: pulmonary stenosis and an interventricular septal defect. However, because there are equal pressures in the two ventricles flow across the defect is negligible. Assuming flow from the right ventricle into the over-

riding aorta to be noiseless, the murmur is therefore that of pulmonary stenosis. Confusion may thus result in differentiating tetralogy from severe pulmonary stenosis with right-to-left shunt through a patent foramen ovale, since in both conditions there is a pulmonary systolic murmur and cyanosis. There are several points, however, which serve to differentiate the two conditions. The murmur of tetralogy tends to be, though not always, less intense than that of pulmonary stenosis (57). This is due to the additional avenue (overriding aorta), through which blood escapes. Also, because of this, there is less resistance to ejection and consequently the murmur is shorter (19, 108, 109) and ends clearly before the second sound. Of even greater importance is the character of the second sound in the two conditions. In tetralogy, due to a marked decrease in flow across the pulmonary valve associated with the pulmonary stenosis, the second sound is usually single (aortic) and often loud. Phonocardiographic studies in pure pulmonary stenosis, on the other hand, revealed that wide splitting of the second sound can be demonstrated in about 85 per cent of the patients (57). The pulmonary component is soft and often inaudible, and the aortic component is not accentuated, often being embraced by the murmur. A pulmonary early systolic ejection sound is infrequent in tetralogy, but is occasionally noted in severe pulmonary stenosis. With the aid of phonocardiography alone, one may therefore differentiate these two lesions.

Eisenmenger's Syndrome (Plate 14, *A* and *B*)

It has been too frequently stated that auscultation is of little value in congenital heart disease. Perhaps this misconception grew from the fact that many different lesions give similar auscultatory findings. A physiologic explanation for this has been offered by Wood *et al.* (126). They suggest that a common hemodynamic situation occurs in almost any congenital heart lesion leading to increased pulmonary vascular resistance, and define this as the Eisenmenger syndrome or pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at aortopulmonary, ventricular, or atrial level. Thus, it is not unexpected that among this group of congenital lesions there will be similarities in the clinical features, including auscultatory findings. The most common congenital lesions producing the Eisenmenger syndrome are: patent ductus arteriosus, ventricular septal defect with and without overriding aorta, and common A–V canal. It may also be caused by ostium secundum defects, transposition of the great vessels (with ventricular septal defect), corrected transposition of the great vessels (with ventricular septal defect), persistent

truncus arteriosus, aortopulmonary septal defect, single ventricle, partial and total anomalous venous drainage, and mitral atresia.

Common to all groups with this syndrome are a loud pulmonary ejection click, a short pulmonary systolic murmur, an accentuated pulmonary component of the second sound, and a loud or soft pulmonary diastolic murmur (Plate 14 *B*). In all, the auscultatory signs of tricuspid incompetence may develop. What then are the *distinguishing features* of the individual lesions?

In patent ductus arteriosus and aortopulmonary septal defects there is clear splitting of the second sound which widens on inspiration. The continuous murmur is usually absent when pulmonary hypertension develops.

A single second sound is often a feature of ventricular septal defect and Eisenmenger's complex itself, and is also found in truncus arteriosus, transposition of the great vessels, and corrected transposition.

Wide splitting occurs in atrial septal defect, total or partial anomalous *pulmonary venous drainage, single atrium*, or common A-V canal.

It is in this group of congenital lesions that phonocardiography and auscultation may be nondiagnostic; however, often positive information is obtained merely by excluding the presence of other lesions.

Pericarditis (Plate 8, *C* and *D*)

The sounds in chronic constrictive pericarditis differ from those in acute pericarditis.

Chronic constrictive pericarditis.—In this form, tight adhesions of the parietal and visceral pericardium obliterate the pericardial space and there is no pericardial friction rub. Not infrequently, systolic clicks are noted. A pathognomonic sign is the early diastolic sound which *corresponds to the nadir of the early diastolic dip of the right ventricular* pressure curve (67, 81). This sound, caused by an abrupt halt in the right and left ventricular filling, is therefore a "water-hammer" phenomenon. It may begin only 0.08 second after the second sound and be mistaken for a snap due to mitral stenosis (in Plate 8, *D*, at 0.09 second).

These hemodynamic and clinical features may be simulated by other restrictive diseases, such as amyloidosis, endocardial sclerosis, diffuse myocardial fibrosis, and occasionally congestive heart failure (68, 69). The heart sounds are occasionally distant, P_2 is frequently accentuated, and significant murmurs are unusual.

Acute pericarditis.—The presence of a friction rub is essential for the diagnosis of acute pericarditis. No distinction in regard to the

etiology can be made on the basis of the friction rub alone. A loud rub may be heard in the presence of a considerable amount of pericardial fluid.

The pericardial friction rub has a leathery, scratchy, or grating quality, and the intensity may vary greatly. It seems more superficial than a murmur and firm pressure on the stethoscope gives the illusion of bringing the sound closer to the ear. Ordinarily, there are two components to a pericardial rub, and when both the "to" and the "fro" components are heard the diagnosis is easy. Both components may be confined to systole or one may be in diastole. Additionally, a presystolic rub may be audible. Not infrequently, the presystolic component is the only one heard (Plate 8, *C*).

In general, rubs tend to be transient and may vary greatly, depending on body position or phase of respiration. When a rub is suspected, auscultation should be done in the supine, sitting, and lateral position, as well as in expiration, inspiration, and during quiet respiration.

Graphically, rubs appear as murmurs but they are never pansystolic. They are usually mid- or late systolic, and are often initiated by a click. The "fro" component may be systolic, or early to mid-diastolic. There is a distinct interval between a presystolic friction rub and the first sound, a feature which serves to differentiate it from the presystolic murmur of mitral stenosis.

Arrhythmias

When the normal sequence of contraction of the atrium and ventricle is altered (due to complete or incomplete heart block, nodal rhythm with retrograde atrial conduction, atrial flutter, or atrial fibrillation), there are changes in the heart sounds which suggest or are pathognomonic of certain arrhythmias.

Atrial fibrillation (Plate 11, *B*).—Since the atria are in a constant state of fibrillation, there are no sounds incident to atrial activity. The length of diastole varies, however, and the loudness of the first sound is thereby affected. If there is a normal diastolic interval, ventricular filling is complete, the A–V valves are almost opposed at the time of ventricular contraction, and a normal first sound is heard (provided no other conditions which alter the first sound, such as mitral stenosis or right bundle-branch block, are present). With a short diastole, ventricular contraction occurs at the time of rapid ventricular filling when the A–V valves are widely open, and a loud first sound is produced. The converse is true with an exceptionally long diastolic interval (96). However, this is not invariably true; we have frequently

observed exceptions to the latter, which is difficult to explain on a physiologic basis (75).

ATRIAL FLUTTER.—In this condition, the atrial rate is more rapid than that of the ventricles by a constant multiple. Not infrequently, the atrial contractions are audible and are frequently recorded on the phonocardiogram. Multiple low-frequency sounds are recorded, one following each flutter wave of the ECG. The changing intensity of the first heart sound may be striking (5, 44). A diagnosis of flutter may therefore be made on the basis of auscultation alone.

NODAL RHYTHM.—This may be of three types: high, mid-, or low nodal. In the last, retrograde atrial conduction is delayed and atrial contraction follows ventricular contraction. Rarely, one hears or can record the atrial contraction which occurs early in systole and is mistaken for an ejection sound, split first sound, or systolic gallop.

COMPLÈTE HEART BLOCK (Plate 15).—Because of the chance relation of atrial and ventricular contraction, the intensity of the first sound varies markedly according to the preceding P–R interval in complete heart block. This explains the "bruit de canon" phenomenon, and the phonocardiogram documents the expected finding of the loud first sound associated with the short P–R intervals. The atrial contraction may be audible, depending on its location in the cardiac cycle. It may be heard as a distinct sound or it may even cause a murmur (atriosystolic murmur) due to ejection of blood from atrium to ventricle (106) (Plate 15, *A*). Because of the large stroke volume associated with slow heart rates, a systolic murmur related to ejection is common (51). A third sound or mid-diastolic murmur (97) occurs due to an increased volume of blood filling the ventricle. The intensity of the atriosystolic murmur varies with the A–V filling gradient, being loudest in early diastole when there is the largest gradient, and softer in late diastole when there is a smaller pressure difference between the atrium and ventricle (106).

WOLFF-PARKINSON-WHITE SYNDROME (Plate 2, *C*).—This is mentioned because, contrary to the expected finding of a loud first sound associated with a short P–R interval, a sound of normal intensity is heard. This may be explained on a physiologic basis, studies by several investigators having indicated that the ventricles do not contract prematurely. The short P–R interval is due to an alteration of the normal activation process, but apparently does not affect the relation of atrial and ventricular contraction (59) (Plate 2, *C*). The intensity of the first sound is increased in the syndrome of short P–R interval, normal QRS complex, and paroxysmal, rapid heart action (60).

TACHYCARDIA.—In many patients with tachycardia (sinus and par-

oxysmal supraventricular), the first sound is loud, whereas in others it is diminished or normal. This is not strictly a rate phenomenon or necessarily related to the P–R interval. Apparently, many factors, including the state of the myocardium, are responsible for the variation in intensity of the heart sounds with tachycardia. In ventricular tachycardia, the first heart sound is often faint; a changing intensity of the first sound is also found.

PREMATURE BEATS.—Whether atrial, ventricular, or nodal, premature beats also affect the intensity of the heart sounds. The most important factor is the degree of prematurity, although loud first sounds are more commonly associated with the atrial variety. For example, premature beats may be so weak hemodynamically that the ventricular pressure does not rise enough to open the semilunar valves and no pulse is felt (frustrate beat). A feeble first sound may be heard, but since the semilunar valves do not open there is no second sound. On the other hand, the first sound may be much louder than normal, in which case the contraction probably occurs at the time of rapid ventricular filling when the A–V valves are open widely. In ventricular premature beats, because of a compensatory pause allowing more complete filling of the ventricle and a larger stroke volume of the succeeding beat, an ejection systolic murmur may be audible during the systolic interval after the compensatory pause. Splitting of the sounds incident to a premature beat are common in the ventricular variety, due to asynchronous contraction of the ventricles (68).

INTRACARDIAC PHONOCARDIOGRAPHY (PLATE I, B)

The most recent contribution to the field of phonocardiography is intracardiac phonocardiography. Obviously, more detailed information about the origin of heart sounds and their relation to hemodynamic events would be obtained by placing the recording instrument at the source of the sounds. Several groups of investigators have studied heart sounds recorded from the various cardiac chambers (78, 105, 110). In addition, in experimentally produced valvular lesions of both sides of the heart, and in left and right heart catheterization, sounds and murmurs can be correlated with the mechanical and electric events of the cardiac cycle (41, 79).

Studies in both dog and man have corroborated many of the concepts about the origin of heart sounds. For example, in the dog with an open chest and a microphone in the left atrium, four distinct sounds can be identified. Events occurring in the right side of the heart are greatly attenuated and not recorded in the left heart. A dis-

tinct atrial sound is always present. The first sound as recorded in the left atrium has two components. The first component starts at the time the left atrial pressure curve crosses the left ventricular and hence is caused by mitral valve closure; the second occurs at the time the left ventricular pressure curve crosses the aortic and therefore is due to aortic valve opening. The second sound recorded in the left atrium is single and corresponds to the incisura of the aortic pulse (aortic valve closure). The third sound occurs on the downstroke of the V wave of the left atrial pressure curve.

In experimental aortic and pulmonary stenosis, typical diamond-shaped ejection murmurs were produced. Of great clinical importance is the fact that moderate aortic stenosis caused a louder murmur than severe stenosis, because forward flow is markedly reduced in the latter condition.

In experimental mitral stenosis, the intensity of the presystolic murmur varied proportionately with the end diastolic A–V pressure gradient.

In a case of proved constrictive pericarditis, the early diastolic sound recorded with a phonocatheter in the right ventricle corresponded to the nadir of the early diastolic dip in the right ventricular pressure curve. This finding supports the probability that the sound is due to the rapidly filling ventricle suddenly being restricted from further filling by the constricting pericardium (79).

At the present time, intracardiac phonocardiography is still in a research stage. Technical difficulties must be overcome and the intracardiac microphones are sensitive and fragile. With this technic, however, the origins of sounds and murmurs may be precisely localized and it is conceivable that intracardiac phonocardiography may become a valuable diagnostic tool. Its usefulness in the understanding of the genesis of heart sounds and murmurs in relation to hemodynamic events has already been proved.

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Diagnosis and Management of the Curable Forms of Hypertension

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THE CAUSE OF hypertension is demonstrable in approximately 20 per cent of patients with elevated blood pressure. The etiology of these "secondary" forms of hypertension can be traced to disease of the kidney (unilateral or bilateral), aorta (coarctation), adrenal medulla (pheochromocytoma) or cortex (Cushing's syndrome or primary aldosteronism), occasionally the brain, and possibly the placenta (toxemia of pregnancy) (Table 1). In the remaining 80 per cent, the cause is not known and the disease has been designated "primary" or "essential" hypertension, or "hypertensive cardiovascular disease," although increasing attention has been devoted to the possible role of the kidney in pathogenesis (7).

The manifestations of primary and secondary hypertension are in general similar, consisting of those attributable mainly to elevation of blood pressure and those attributable mainly to associated atherosclerotic vascular insufficiency (Table 2) (58). The latter are also due in part to the elevated blood pressure, which accelerates the development of vascular change. Any of the forms of hypertension, with the exception of that due to coarctation of the aorta, may enter an "accelerated" or "malignant" stage, characterized by sustained, marked elevation of the diastolic blood pressure, with papilledema, and later encephalopathy and rapidly progressive renal insufficiency. In both primary and secondary hypertension, the blood pressure can be lowered by antihypertensive drugs and other measures employed in management of the disease (Table 3) (58), although these are generally less

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severity, at any age, the possibility of a superimposed etiologic factor such as renal arterial obstruction should be considered.

Several forms of secondary hypertension are amenable to surgical cure, particularly unilateral or occlusive vascular renal disease, coarctation, pheochromocytoma, Cushing's syndrome, and primary hyperaldosteronism. The examination of every hypertensive patient must include means of excluding these curable forms of the disease. It is important that curative measures be instituted before the hypertension has resulted in irreversible renal vascular changes which may perpetuate the hypertension despite removal of the original exciting agent.

TABLE 3—MEANS OF CONTROLLING ELEVATED BLOOD PRESSURE

DRUGS	OTHER MEASURES	MECHANISM
Sedatives; alkaloids of rauwolfia, veratrum, & ergot	Rest; psychotherapy	Reduction of central vasoconstrictive activity
Chlorothiazide	*Salt restriction; weight loss*	?
Hydrazinophthalazine[a]		Direct vasodilatation
Hexamethonium; pentapyrrolidinium[b]; mecamylamine[c]; chlorisondamine[d]	Sympathectomy	Ganglionic block

[a] Apresoline; [b] Ansolysen; [c] Inversine; [d] Ecolid.

UNILATERAL OR OCCLUSIVE VASCULAR RENAL DISEASE

Goldblatt's observation in 1934 that constriction of the blood supply to one kidney results in hypertension in experimental animals led him to an intensive search for patients with hypertension and unilateral renal disease in whom nephrectomy might relieve the hypertension (52). Many patients were subsequently identified in whom hypertension was caused by a lesion impairing the blood supply to one or both kidneys, and were cured by restoration of normal blood flow or by removal of the affected kidney. It has been estimated that between 1 and 5 per cent of hypertensive patients have unilateral renal disease amenable to surgical cure (144, 145). In one clinic, this etiology was recognized ten times more frequently than pheochromocytoma (19). However, the identification of patients with unilateral or occlusive vascular renal disease in whom operation should be performed has proved to be an exacting task. Reliance on the degree of functional impairment of the offending kidney has not been particularly helpful (169). Some of the best results have occurred after the removal of a kidney that had

TABLE 1.—CAUSES OF HYPERTENSION

Site	Disorders: Not Associated with Preceding Renal Disease	Disorders: Associated with Preceding Unilateral or Bilateral Renal Disease
Kidney	(?) Primary (essential) hypertension	Primary renal disease (pyelonephritis, glomerulonephritis, polycystic disease), occasionally amyloidosis
Renal artery and its branches	—	Occlusive vascular disease (atherosclerosis, thrombosis, embolization, infarction, aberrant renal artery)*, periarteritis, occasionally lupus erythematosus, heart failure
Urinary tract	—	Obstruction (stricture, stone, prostate, tumor)*
Aorta	Coarctation*	—
Adrenal medulla	Pheochromocytoma*	—
Adrenal cortex	Cushing's syndrome*	—
	Primary hyperaldosteronism*	—
Placenta (?)	(?) Toxemia of pregnancy*	—
Midbrain	Tumor, poliomyelitis, encephalitis, porphyria	—

* Curable forms of hypertension.

TABLE 2.—MANIFESTATIONS OF HYPERTENSIVE DISEASE

Site	Manifestations: Due Mainly to Hypertension	Manifestations: Due Mainly to Vascular Insufficiency
Brain	Headache; giddiness; encephalopathy; hemorrhage	Thrombosis
Cardiovascular system	Epistaxis; left ventricular enlargement and failure	Angina; infarction; right ventricular enlargement and failure
Retina	Hemorrhages; exudates; papilledema	Arteriosclerosis; occlusion
Kidney	—	Insufficiency

effective in secondary hypertension, particularly that due to renal disease (8) and pheochromocytoma.

Primary hypertension generally begins between the age of 25 and 50 years in persons with a family history of the disease. When the blood pressure becomes elevated before the age of 25, or after 50, and when the antecedents have been normotensive, a specific cause can usually be found. When primary hypertension suddenly increases in

artery, arching around the renal vein, is reported to be found in 3 per cent of routine autopsies, and may be responsible for some instances of orthostatic hypertension, as well as of orthostatic proteinuria (109).

Hypertension is less likely to occur after obstruction of the renal artery or its branches by an embolus than by a thrombus, but occasional instances of hypertension have been attributed to embolized mural thrombi, atheromatous plaques (63) or bacterial vegetations, or to paradoxic emboli (48). Thrombosis of the renal veins produces a clinical picture dominated by marked albuminuria, hypoalbuminemia, and edema (the nephrotic syndrome) (121); but in half the patients some hypertension develops (66, 78).

Hypertension associated with unilateral pyelonephritis is less uniformly ameliorated by nephrectomy than is that due to obstructive renal vascular disease (154). Those patients who do respond to this procedure are reported to have atrophic tubular acini of the ischemic type in the affected kidney (19), suggesting that the hypertension may be due to vascular obstruction rather than to parenchymal disease alone (79). Renal hypogenesis may be associated with hypertension, usually as a result of superimposed pyelonephritis. Hypertension may also occur as a result of renal compression from a subcapsular hematoma, and may be relieved by nephrectomy (34). Hydronephrosis (70), renal tuberculosis (87), and tumor (31) are uncommon causes of hypertension, and only occasionally does nephrectomy lower an associated elevation of blood pressure.

There are other causes of renal hypertension, such as glomerulonephritis, polycystic disease, periarteritis, intensive irradiation (164), and occasionally amyloidosis or disseminated lupus erythematosus, but both kidneys are generally affected and unilateral nephrectomy is rarely warranted, unless the organ can be replaced by a normal kidney from an identical twin (101).

Clinical Manifestations

The hypertension in patients with unilateral or occlusive vascular renal disease is usually, though not always, of abrupt onset, with a high, fixed diastolic pressure and rapid progression of all the clinical manifestations, particularly headache and retinopathy (19, 72, 119). The disease usually occurs in persons with previously normal blood pressure, but may be superimposed on benign essential hypertension, as illustrated by case 1, described later. Approximately half the patients progress rapidly to the malignant stage, with papilledema and albuminuria. Some patients are reported to have leukocytosis, and

relatively good function and configuration, sufficient to give a normal intravenous and retrograde pyelogram. In a recent review of 575 nephrectomies for hypertension, the blood pressure remained normal for a year after operation in only 26 per cent (145). However, by careful attention to the patient's history and to the results of differential renal function tests and aortography, the proportion of operative cures can be increased (19, 122).

Mechanism of Hypertension

The commonest cause of correctable renal hypertension is unilateral obstruction of the renal artery. Less common causes are bilateral renal arterial obstruction, unilateral parenchymal disease, particularly pyelonephritis, and unilateral pericapsular disease. It has been suggested that reduction in arterial pressure or blood flow in one or both kidneys may result in release of a pressor polypeptide, angiotensin (7). It is generally believed that hypertension develops only if there is ischemia of viable tubular tissue, which becomes atrophic (19). Complete infarction or destruction of one kidney does not cause hypertension, and removal of a kidney that functions little or not at all is not likely to affect existing hypertension (150). In most cases of localized renal infarction, hypertension does not develop, perhaps because there is usually a sharp demarcation between the infarcted area and healthy surviving tissue without an intermediate zone of atrophic but viable tubules. Localized infarction is more likely to cause hypertension in young persons, possibly because they have better collateral circulation (104).

The commonest cause of obstruction of the renal artery or its branches is intimal atherosclerosis, with or without thrombosis. Less often, the artery may be obstructed by thrombosis of a renal arterial aneurysm, traumatic thrombosis (particularly during operative procedures) (99), syphilitic arteritis, thromboangiitis, or idiopathic thrombosis, or by pressure from a hematoma, arteriovenous fistula (102), or extrinsic tumor (26). The orifice of the renal artery may be obstructed by a plaque or an ascending thrombus (14) in the aorta, as in Leriche's syndrome (45), or rarely, by a descending thrombus or intravascular tumor. Congenital stenosis is much less common than the acquired form. The stricture may be confined to the renal artery, or it may result from coarctation of the abdominal aorta. It may be single or multiple, and may be accompanied by congenital renal arterial aneurysms. An aberrant renal artery or vein may occasionally result in impairment of the vascular supply. An aberrant inferior polar renal

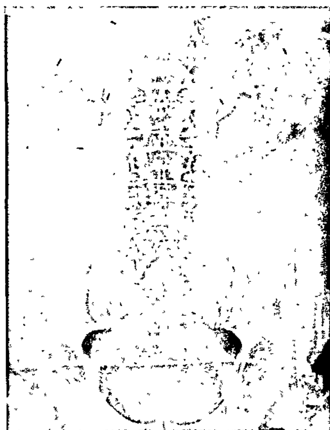


PLATE 1.—Intravenous pyelogram (Case 1), showing reduced size of right kidney; borders of kidney have been marked.

some polyuria, polydipsia, and impaired concentrating power (95). Others are said to have an overwhelming inner tension and restlessness (6). Those patients in whom the disease is due to thrombosis or embolization of the renal artery may give a history of recent abdominal pain suggesting renal colic or appendicitis, and they may have had a normal appendix removed. Any recent trauma to the renal region, accidental or surgical, raises the possibility of renal artery thrombosis or subcapsular hematoma.

The longer the duration of the hypertension beyond a period of 1 year, the less likely is nephrectomy to produce a cure. Nevertheless, successful nephrectomy has been performed in several patients after 2 years of hypertension (19), and in 1 patient after 7 years (128).

The finding of an audible bruit over one or both femoral arteries, indicating the presence of atherosclerosis, is said to make the possibility of concomitant renal atherosclerosis more likely (6).

Diagnosis

The initial problem in diagnosis is the selection of those patients with hypertension in whom there is sufficient suspicion of unilateral or occlusive vascular renal disease to justify differential renal function tests and angiography. These procedures are not lightly undertaken, as they not only cause discomfort, but the former may introduce infection and the latter may, in rare instances, produce renal or spinal cord damage. The next problem is evaluation of the information obtained, and, finally, the decision concerning operative intervention and choice of procedure.

Pyelography.—Every patient with hypertensive disease and adequate renal function deserves to have intravenous pyelography as part of the initial examination. If both kidneys are not demonstrated, retrograde pyelography may be performed. In about 50 per cent of the patients with hypertension due to unilateral renal disease, the affected kidney is over 1 cm. smaller than opposite one (Plate 1). Kidney shrinkage over months is also significant. Serial x-rays every minute for 5 minutes may show delayed excretion on one side. Failure to visualize a kidney later seen in normal retrograde polygram suggests an obstruction of the renal artery. However, in nearly half the patients with unilateral renal disease, and in most of those with bilateral disease of the renal arteries, a normal intravenous pyelogram bilaterally is obtained, so that this finding by no means excludes correctable renal hypertension. The use of Diodrast-I^{131} (167) has not greatly improved the value of the procedure.

Total renal function tests.—These are of no value in diagnosis,

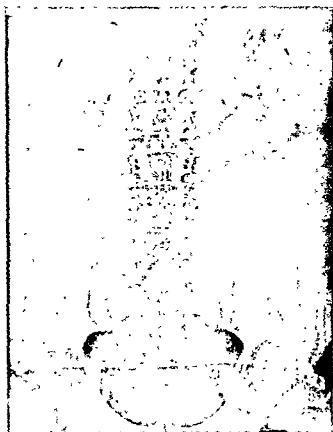


PLATE I.—Intravenous pyelogram (Case 1) showing reduced size of right kidney; borders of kidneys have been marked.

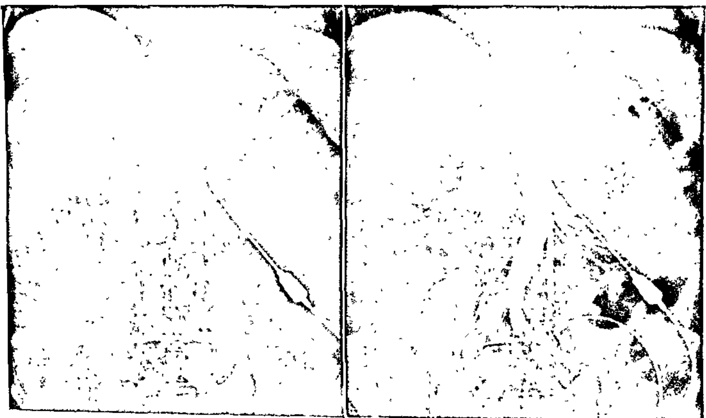


PLATE 2.—Angiograms (Case 1) taken 1 and 2 seconds, respectively (*left* and *right*), after injection of radiopaque dye into the aorta just above level of renal arteries, showing persistent obstruction to flow of dye into right renal artery.

except that patients with marked diminution in total renal function are not suitable for nephrectomy. However, nephrectomy has been employed in a few patients with moderate reduction in total renal function (72), resulting in disappearance of hypertension, and, in 1 patient, of azotemia and albuminuria as well (75). Relief of severe *hypertension may slow the progress of renal disease, whether unilateral* or bilateral, and may occasionally result in some return of renal function (106).

DIFFERENTIAL RENAL FUNCTION TESTS.—These are carried out after introduction of a cystoscope and of temporary indwelling ureteral catheters. Next to angiography, this is the most useful means of detecting obstructive lesions of the main renal artery. However, because changes in function vary with the location of the occlusion, the tests alone have not yet proved to be a completely reliable means of predicting whether or not *nephrectomy will result in amelioration* of hypertension. The tests are seldom helpful in detecting lesions of a branch of the main renal artery, bilateral renal arterial disease, or unilateral pyelonephritis. Furthermore, there is *still* insufficient data on differences in function of opposite kidneys in essential hypertension, and lack of agreement on the precise functional pattern of the kidney which should be removed to cure hypertension. Hence, differential renal function tests can only establish a presumptive diagnosis of hypertension due to unilateral renal disease, and should serve as one of the indications for aortography.

The most constant finding in hypertension due to unilateral renal disease is a low volume of urine on the affected side (72). However, the vagaries of ureteral irritation and spasm are such that this measurement alone does not suffice, and must be supplemented at least by measurement of sodium concentration. Connor and associates (19) have demonstrated that reduction in urinary flow by at least 50 per cent and in sodium concentration by at least 15 per cent strongly suggests unilateral renal disease attributable to reduction in renal arterial pressure. Birchall and co-workers (6) have confirmed this, but have also demonstrated that variation in urinary flow may occasionally result in the difference in sodium concentration between the two sides being less than 15 per cent in patients whose hypertension was subsequently cured by nephrectomy; in 1 of their patients, the concentration was higher on the affected side. Their data indicate that a more refined measurement is that of the fraction of filtered sodium and water reabsorbed by the renal tubules. In the presence of unilateral renal disease, there is generally an increased proportion of water and *sodium reabsorbed*, and *hence a decreased proportion* rejected by the renal tubules. This is illustrated by the 2 cases later described (Table

4). It is not clear whether this change is due to reduced renal arterial pressure, decreased renal tubular load, or decreased delivery to the renal tubules of the hormones responsible for reabsorption of salt and water. The former explanation seems more likely, since the gradual diminution of the caliber of one renal artery results, in experimental animals, in reducing urinary volume and sodium excretion and con-

TABLE 4.—Results of Differential Renal Function Tests in 2 Patients Whose Hypertension Was Later Ameliorated by Removal of Right Kidney (Case 1) and Left Kidney (Case 2)

Function Tested	Case 1			Case 2		
	Left Kidney	Right Kidney	Right/Left X 100%	Left Kidney	Right Kidney	Left/Right X 100%
Renal plasma flow, ml./min.	114	44	42	109	88	124
Glomerular filtration rate, ml./min.	35	12	29	25	20	125
Filtration fraction	0.30	0.28	93	0.23	0.23	100
Urine flow, ml./min.	3.4	0.2	6	0.6	1.2	50
Sodium clearance, ml./min	2.2	0.1	4	0.5	1.0	50
Potassium clearance, ml./min.	30.4	5.6	18	2.0	3.5	57
Urine sodium conc., mg./ml.	2.1	1.6	76	2.7	3.0	90
Urine potassium conc., mg./ml.	1.2	4.1	342	0.39	0.37	105
Filtered load reabsorbed, %						
Water	90.3	98.5	109	97.4	93.9	104
Sodium	93.9	99.3	106	98.0	94.5	104

centration on the ischemic side before there is any measurable reduction in renal blood flow or filtration rate (107, 162).

Schlegl and associates (137) have reported a different pattern of urinary excretion in patients with proved unilateral renal hypertension, consisting of lower volume, and higher osmolarity, potassium and ammonia concentration, and pH of the urine from the affected side. The sodium concentration on the affected side was found to be variable, and in only 1 out of 5 patients was it more than 15 per cent below that on the opposite side.

The renal blood flow and filtration are usually, but not invariably, reduced on the involved side in patients with hypertension due to unilateral renal disease. Thus, in case 1 they were reduced, but in case 2 they were higher on the affected side (Table 4). Changes in renal blood flow and filtration rate are not specific, being found in other forms of renal disease as well. However, the finding of an increased urine-plasma inulin ratio and decreased urinary flow on one side is said to be suggestive of unilateral renal arterial obstruction (6).

Aortography.—This procedure is the most accurate means of de-

tecting renal arterial obstruction or anomaly. Hypaque sodium, 10 to 20 ml., is administered by translumbar injection into the aorta, under local anesthesia, above the level of the renal arteries through a large bore 18 gauge needle. Injection may also be made through a radiopaque catheter directed into the aorta from the femoral artery (57). Since the dye induces renal vasoconstriction, which may last up to 3 days, it is best to do this procedure after the differential renal function tests, or not less than 3 days before (6).

Aortography may reveal obstruction in the renal artery (Plate 2), the presence of collateral circulation and, sometimes, poststenotic dilatation or aneurysm. When unilateral or bilateral renal arterial obstruction is demonstrated, aortography alone is reliable enough to justify surgical exploration. When the stenosis is questionable, the results of differential renal function tests must also be considered. The presence of stenosis can also be confirmed by measurement of the arterial pressure proximal and distal to the suspected stenosis at the time of operation, provided that the length and condition of the renal artery permit this procedure.

Aortography involves a slight, but definite, risk. The injection of too much dye, or too high a concentration, directly into a renal artery, may cause renal injury and insufficiency which may be fatal (55). Thrombosis of mesenteric arteries and transverse myelitis have also been observed (97). To avoid injection of dye into a renal or mesenteric artery, or into kidney tissue, a scout film is taken after injecting a small amount to check the position of the needle or catheter.

Other procedures.—Brust and Ferris (8) have reported that the *failure of the blood pressure to fall, or the occurrence of a pressor response*, after administration of a ganglionic blocking agent, such as tetraethylammonium chloride suggests that hypertension is of renal origin and may be reversed by nephrectomy.

Renal biopsy has unfortunately been of no help in diagnosis. While the presence of atrophic tubular acini is considered by some to be diagnostic of renal ischemia (19), the lesions are usually restricted and localized.

Management

In the management of occlusive lesions of the renal artery, surgical arterial reconstruction is preferable to nephrectomy, whenever possible, since the affected kidney frequently functions well and may be the better of the two kidneys. Unfortunately, endarterectomy is a difficult procedure and not often successful. Arterial homografts are the treatment of choice for occlusive disease of one or both renal arteries, and

have been successfully employed (73, 123). Splenorenal anastomosis may be employed for lesions of the left renal artery. If arterial reconstruction cannot be done, or if the kidney is severely damaged, partial or complete nephrectomy is performed. Partial nephrectomy, i.e., segmental nephrectomy of a pole, or sagittal heminephrectomy, may be performed when there is occlusion of a main branch or of an accessory or reduplicated renal artery (62). If these procedures cannot preserve functioning renal tissue, nephrectomy is necessary.

Illustrative Case Histories

Case 1.—W.F., a 58 year old white man, was known to have had asymptomatic mild hypertension for at least 5 years. In 1953, his blood pressure was 170/104 mm. Hg. In July, 1955, he began to have blurring of vision, and his blood pressure was found to be 270/140. He was given antihypertensive drugs without relief of his visual disturbance. In March, 1956, he began to have giddy spells, moderate exertional dyspnea, nocturnal dyspnea, palpitations, intermittent precordial pain radiating to the left arm, and evening ankle edema.

Physical examination revealed a blood pressure of 240/140 mm., grade IV retinopathy with papilledema, hemorrhages, exudates, marked arteriosclerotic changes, moderate enlargement of the heart to the left with boot-shaped configuration, presystolic gallop rhythm, systolic apical blowing murmur, accentuated second heart sound, slight hepatic enlargement, and strong femoral pulses.

Urinalysis revealed a 2+ proteinuria. Blood nonprotein nitrogen was 45 mg. per 100 cc. Serum electrolytes and blood counts were normal. Phenolsulfonphthalein (PSP) excretion was 25 per cent in 15 minutes and 50 per cent in 2 hours. Urea clearance was 50 per cent of normal. The phentolamine test result was negative. The ECG showed evidence of left ventricular hypertrophy. An intravenous pyelogram (Plate 1) disclosed the right kidney to be significantly smaller than the left. Differential renal function tests (Table 4) showed a marked right-sided decrease in renal blood flow, filtration rate, sodium and water excretion, and, to a lesser extent, sodium concentration, with increased renal tubular reabsorption of sodium and water on that side. An aortogram disclosed evidence of obstruction to the flow of dye in the right renal artery (Plate 2).

The patient was digitalized and put on a low sodium diet, and on May 16, 1956, a right nephrectomy was performed. The right kidney was moderately small. After the operation, the blood pressure fell to 170/90 mm. and has remained between that level and 180/104 ever since. The vision and eyegrounds gradually improved, with disappearance of the papilledema and hemorrhages. The patient became asymptomatic and has remained so. PSP excretion and urea clearance fell slightly after the operation, but subsequently returned to the original values. Histologic examination of the kidney showed marked arterial and moderate arteriolar nephrosclerosis.

Case 2.—G.S., an 8 year old white boy who had always enjoyed good health,

fell and fractured his left wrist in April, 1957. During anesthesia for reduction of the fracture his blood pressure rose from 120/80 to 225/190 mm. Hg. After the operation his blood pressure remained at about 210/140 mm. Hg. The only other findings on physical examination were multiple subcutaneous nodules and café-au-lait spots. The intravenous injection of phentolamine caused the blood pressure to fall to 168/90 for several minutes. The urinary excretion of catechol amines was 120 mg. per 24 hours, which is above the upper limit of normal. An intravenous pyelogram showed the left kidney to be slightly smaller than the right. Results of other routine laboratory studies were not informative.

Despite the presence of neurofibromatosis, onset of hypertension during anesthesia, positive phentolamine test result, and moderately increased urinary excretion of catechol amines, all suggesting the presence of a pheochromocytoma, differential renal function studies were carried out (Table 4). The renal blood flow and glomerular filtration rate were slightly greater on the left side, but the sodium concentration was slightly lower and the sodium and water excretion moderately lower on this side. The renal tubular reabsorption of sodium and water were greater on the left side. An aortogram showed 3 distinct renal arteries coming off the aorta on the left side. This was confirmed at operation. Except for some fetal lobulation, the left kidney looked grossly normal, as did the adrenals. The left kidney was removed. During the next hour, the blood pressure fell to 110/70 mm. and has remained normal since then. Histologic examination of the kidney revealed only inflammatory changes in the glomeruli.

COARCTATION OF AORTA

Coarctation of the aorta is a congenital abnormality in which the aorta is narrowed or occluded, usually near the origin of the ductus arteriosus, or occasionally elsewhere in either the thoracic or abdominal aorta.

Clinical Manifestations

As a rule, the arterial pressure is elevated above the constriction, and may be high, normal, or low distally. Occasionally, the blood pressure is normal above the constriction (135). Enlarged collateral arteries develop, connecting the main branches which join the aorta above and below the constriction.

The disease is five times as common in males as in females. It is often associated with other cardiovascular defects, particularly congenital bicuspid aortic valve (40 per cent), patent ductus arteriosus (13 per cent), and stenosis of the aortic valve (5 per cent) which may calcify (13). Aneurysmal dilatation of the aortic sinuses (Valsalva) occurs occasionally (151).

In uncomplicated coarctation, a systolic murmur is usually heard,

beginning in early systole and clearly separated from the first sound. This murmur is believed to arise from the collateral channels and from the aorta below the coarctation (147). It is usually best heard on either side of the lower sternum at the level of the second to fourth interspaces over the internal mammary arteries, and over the enlarged collaterals in the back, particularly between the scapulae. It differs in timing from the systolic murmur of aortic stenosis, which occurs in 5 per cent of patients (13) and which begins without separation from the first sound. If the coarctation is 3 mm. or more in diameter, the systolic murmur usually does not extend beyond the second sound, but if it is smaller, a continuous murmur arising from the aorta may be heard over the spine between the scapulae. The diastolic component of the continuous murmur may lead to the mistaken diagnosis of aortic regurgitation. Mild regurgitation does occur in one-fourth of the patients, and is usually attributed to atherosclerosis of a bicuspid valve. The resulting diastolic decrescendo murmur is not transmitted to the back and differs by its unique pitch and quality from the continuous murmur of coarctation.

The complications of coarctation consist of rupture of the aorta or of dilated collateral vessels, bacterial endocarditis on a congenital (particularly bicuspid aortic valve) or rheumatic valvular lesion, bacterial endarteritis at the site of constriction, and the complications of hypertension. The latter include congestive heart failure and intracranial hemorrhage, generally from a ruptured congenital (berry) aneurysm. Neurologic complications other than intracranial hemorrhage are rare, but a partial Brown-Sequard syndrome has been reported, attributed to compression of the spinal cord by intramedullary and extramedullary arteries enlarged by the collateral circulation (67). Intermittent claudication occurs only occasionally, since blood flow in the lower extremities is usually normal despite the diminished arterial pulsations. There is only one reported occurrence of ischemic necrosis of the legs (170).

Hypertension due to coarctation of the aorta is the only form in which the accelerated (malignant) phase does not develop, perhaps because the constriction protects the kidneys from the effect of the high blood pressure.

The coarctation is occasionally located in the abdominal aorta, usually at or below the level of the renal arteries. (46). If it involves one or both renal arteries, hypertension due to renal ischemia may be superimposed. In patients with coarctation of the abdominal aorta, a murmur is often heard over the epigastrium, and a pulsation and bruit

may be felt over the lower thorax. These patients are more likely to complain of intermittent claudication of the lower extremities.

In the reverse coarctation (aortic arch) syndrome, thrombotic occlusion of the branches of the aortic arch results in diminution or absence of pulses in the upper extremities, the so-called pulseless disease (61, 130). The thrombosis is sometimes attributed to syphilitic arteritis but is usually of unknown cause. In some patients, hypertension occurs in the lower extremities. The cause of this is not clear; some have ascribed it to cerebral ischemia.

The average age of death in patients with coarctation of the aorta who are not operated on is 35 years. One-fourth of the patients die of rupture of the aorta or dilated collateral vessels; one-fourth of bacterial endocarditis of a congenital or rheumatic valvular lesion, or bacterial endarteritis at the site of constriction; one-fourth of congestive heart failure or intracranial hemorrhage, generally from a congenital aneurysm; and one-fourth from incidental causes.

Mechanism of Hypertension

Since the diastolic pressure is elevated in the lower as well as the upper extremities in 20 per cent of patients with coarctation, it has been suggested that the hypertension may be due to generalized vasoconstriction. In experimental animals, chronic aortic constriction results in generalized hypertension; this has been attributed to renal ischemia, as transplantation of a kidney above the constriction decreases the hypertension (138). However, Culbertson and associates (24) were unable to find evidence of renal ischemia in most patients with coarctation, and attributed the hypertension above the stricture to the mechanical effect of the narrowing, foreshortening of the aortic compression chamber, and increased stroke volume of the left ventricle. Nor were they able to find evidence of the generalized increase in arteriolar resistance which is characteristic of other forms of arterial hypertension.

Diagnosis

The femoral pulses should be carefully palpated in every patient with hypertensive disease. Reduced and delayed femoral pulses should arouse suspicion of coarctation of the aorta, particularly in younger patients in whom arteriosclerotic obliteration of the lower aorta (Leriche's syndrome) is not to be expected.

Neither normal blood pressure in the upper extremities nor pal-

pable femoral pulses excludes the diagnosis of coarctation. Therefore, whenever the femoral pulses are diminished, or a late systolic murmur is heard on either side of the lower sternum or between the scapulae, the difference in pressure between the upper and lower extremities should be determined. The leg blood pressure can be measured by auscultation or palpation, employing a wide cuff for constriction of the thigh. The diagnosis may also be indicated by the detection of enlarged collateral arteries, seen or felt under the skin between and below the scapulae.

Roentgenography.—The most characteristic sign of coarctation of the aorta is notching of the lower border of the posterior aspect of the upper ribs, produced by enlarged intercostal arteries. This is present in 80 per cent of patients with coarctation (37), and in about 5 per cent is the only definite sign of coarctation seen in the posteroanterior view (10). Rib notching usually appears after the age of 10 years, but may be found in children as young as 5. In about a third of the patients, this view also discloses a notch, representing the coarctated segment, in the left border of the descending aorta just above the level of the main pulmonary artery. Sometimes the coarctation is best seen in the oblique view. In about 80 per cent of patients, a barium swallow discloses a deep imprint on the left lateral aspect of the esophagus at the level of the pulmonary artery, due to poststenotic dilatation and kinking of the aorta. Less common roentgenographic features include widening of the left upper mediastinal shadow by a dilated left subclavian artery (55 per cent), left ventricular enlargement (40 per cent), discontinuity between the descending aorta and aortic knob (38 per cent), a small aortic knob (20 per cent), and poststenotic aortic widening or aneurysm (4 per cent) (37).

Roentgenographic signs resembling those of coarctation, and systolic murmurs, may be produced by kinking of the aortic arch (9). In both conditions, some dilatation of the aorta just beyond the anomaly may also occur, resulting in impression of the dilated segment on the barium-filled esophagus. In kinking of the aortic arch, however, there is no change in the blood pressure proximal or distal to the kinking.

When the presence, location, or extent of coarctation of the aorta is not clear, the lesion may be visualized by aortography or angiocardiography. The former gives better visualization, but the risk is slightly greater. For an adult, 20 ml. of 70 per cent Diodrast are injected through a catheter directed into the aorta from the brachial or carotid artery. The tip of the catheter must not be in or near the mouth of the common carotid artery, as injection of concentrated dye into this site may result in convulsions and death. More rarely, the procedure may initiate a dissecting aneurysm or bleeding from the aorta (143).

Management

The stenotic segment can usually be successfully excised and the proximal and distal ends sutured together. A long stenosed segment or degenerative change in the aorta may require the insertion of a preserved aorta homograft or a nylon or dacron sleeve (111). Opinion is divided regarding the relative merits of grafts and prosthetic devices (133). The subclavian artery (139) or a local plastic procedure (110) may also be used when apposition of the proximal and distal aorta is not feasible.

In a cooperative study of 1,601 cases of coarctation of the aorta treated surgically (133), the operative mortality rate was 8.6 per cent, with 38 per cent of the deaths due to heart failure, particularly left ventricular failure with pulmonary edema, 21 per cent due to disruption of the anastomosis, 12 per cent from hemorrhage at the time of surgery, usually from thin-walled dilated intercostal arteries, and 4 per cent each from cardiovascular accidents and necrotizing arteritis. A satisfactory clinical result was obtained in 96 per cent of the survivors. Operative results were most favorable, with a mortality of 6.8 per cent, in patients between the ages of 4 and 15. In the infant to 3 year age group, the operative mortality rate was 16 per cent, and in the group over 30 years it was 11 per cent. Satisfactory relief of hypertension following surgery occurred in 95 per cent, with the blood pressure becoming normotensive in 72 per cent. In only 5 per cent did serious hypertension persist. The incidence of persistent hypertension increased progressively as the patient's age increased.

Since about 60 per cent of patients with coarctation and hypertension die before the age of 40, surgical repair is justified despite the appreciable operative mortality, provided there is no serious contraindication to operation, such as too large an aortic lesion for a graft or prosthesis, serious coexisting disease, or advanced age. The prognosis in patients with mild coarctation and normal blood pressure in the upper extremities is better, and the risk of operation must be weighed against the possible development of the complications of coarctation. Sandifer (135) does not advise operation in these patients. Spencer and associates (147) consider surgery unnecessary if the diameter of the isthmus of the coarctation is greater than 8 mm., since in such cases blood flow is not reduced. If the lumen is less than 8 mm., however, operation is carried out because of the possible development of serious poststenotic aneurysm. If the lumen is 4 to 8 mm., the collateral circulation may not be well developed, and damage to the spinal cord or kidneys may occasionally occur following clamping of the aorta, unless protective measures such as hypothermia or a pump by-pass are used. In

patients over 40 years of age, the operative risk increases, operation in these patients can be avoided if the blood pressure in the upper extremities is normal or only slightly elevated, and if there are good pulses in the lower extremities and no evidence of collateral circulation (113).

Postoperative complications include rupture, aneurysm, or endarteritis of the anastomotic site (96), and persistence or recurrence of hypertension sometimes accompanied by arteritis. In 10 to 30 per cent, the operation is followed in 3 to 5 days by evidence of a necrotizing panarteritis limited to arteries arising below the coarctation, and resembling periarteritis nodosa (64, 126). Immediately after the aortic clamps are released, there is generally an abrupt drop of pressure in the upper extremities to normal or near normal, but, within a short time, usually minutes to hours, the pressure may rise toward the preoperative level. Hypertension may then persist for days, weeks, or months. The sudden rise of intravascular pressure may be responsible for the development of arteritis, which is manifested by local or generalized abdominal pain and tenderness, vomiting, and leukocytosis. Decompression of the bowel with a Miller-Abbott tube and the administration of antibiotics to sterilize the intestine are recommended. In a small number of patients, laparotomy and resection of severely involved intestine are necessary. Some have recommended the administration of antihypertensive drugs postoperatively to prevent or treat the rise in pressure in the lower body segment (64).

PHEOCHROMOCYTOMA

Pheochromocytoma is a tumor of the chromaffin cells of the sympathetic nervous system. The adrenal medulla, more frequently on the right side, is the site of 90 per cent of the tumors, and the same proportion is benign (103). Approximately 10 per cent are bilateral and 10 per cent are extra-adrenal; 10 per cent are malignant. The extra-adrenal tumors occur most commonly in the retroperitoneal tissues of the abdomen, usually near the sympathetic chain and in relation to Zuckerkandel's organ, or in the renal hilum, celiac ganglion, or base of the mesentery. Rarely, they occur in the posterior mediastinum (115) or bladder (124). In 16 per cent of the patients, the tumor is bilateral or multicentric (160). In 5 per cent, the tumor is associated with multiple neurofibromatosis (Recklinghausen's disease), and, less commonly, with other neurocutaneous disorders, such as Lindau-von Hippel disease (51).

The tumor usually manifests itself during adult life, slightly more

often in women than in men, but may occur at any age. Several instances of familial occurrence have been reported (56, 132). In infants and young children, the tumor is often atypical or multicentric. It is estimated that pheochromocytoma may be the etiologic agent in about 1 of every 200 patients with hypertension.

Mechanism of Hypertension

The manifestations of the tumor are due to the secretion of epinephrine or norepinephrine, and are almost entirely referable to the pharmacologic effects of these hormones.

Norepinephrine produces vasoconstriction in skeletal muscle, skin, kidneys and liver, increased blood pressure, bradycardia, sweating, and a slight increase in blood sugar and basal metabolic rate. Epinephrine produces vasoconstriction in skin and kidneys, vasodilatation in skeletal muscle and liver, a slight increase or decrease in blood pressure, tachycardia, sweating, increase in blood sugar and basal metabolic rate, dilatation of pupils, fall in blood eosinophils, and apprehension and excitement (35).

Malignant metastases may also be active secretors (25). Rarely, the tumor may not secrete either hormone, and rarely it may give rise to symptoms due to its increasing size or to metastatic dissemination.

Clinical Manifestations

The manifestations of the disease depend on the amount and proportion of the hormones secreted by the tumor. Any or all of the following changes may occur (35, 160): (1) hypertension, with increase in systolic and diastolic blood pressure, and resulting symptoms, particularly headache; (2) either no change in cardiac rate or tachycardia; (3) increased sweating; (4) cutaneous vasoconstriction, resulting in pallor; (5) increase in fasting blood sugar concentration, sometimes resulting in glycosuria and even diabetes; (6) increase in basal metabolism; and (7) central nervous excitation. In approximately half the patients, the augmented secretion of hormone occurs intermittently, with paroxysms of effector reactions, including hypertension; in these patients, the blood pressure is normal between attacks. In the remaining half, the augmented secretion of hormone is continuous, with persistent hypertension; but even these patients may have periods of further augmentation of hormone secretion and hypertension, with accompanying symptoms (53).

Most patients with paroxysmal hypertension complain of attacks.

Headaches, usually severe, are the commonest symptom; sweating, palpitations and pallor the next commonest; and, in decreasing order of incidence, anxiety, nervousness, flushing of face, nausea and vomiting, precordial pain, abdominal pain, pain and numbness in the legs, tingling and coldness of the hands and feet, tremor, and dizziness. There is also often weight loss. Kvale and associates (83) point out that most patients with pheochromocytoma are thin, particularly those with persistent hypertension. The frequency of attacks varies from as often as 25 a day to once every few months. They usually last about 15 minutes, but may persist from seconds to days. The attacks are followed by weakness and exhaustion. The attacks may recur for months or years before more permanent changes in the cardiovascular system occur, such as persistent hypertension, cerebral hemorrhage or thrombosis, myocardial infarction, and retinopathy.

The complications of hypertensive disease are more likely to occur when the rise in blood pressure becomes sustained, and the disease may enter the accelerated (malignant) phase, with papilledema and eventually encephalopathy and renal insufficiency. The changes in renal function and structure (140), however, are usually less marked than in primary hypertension of comparable severity. In children, polydipsia and polyuria may occur, simulating diabetes insipidus (153).

Sudden death may occur following myocardial infarction, ventricular arrhythmia, or cerebral hemorrhage. Or shock may suddenly appear, with a clinical picture suggesting acute adrenal insufficiency (Waterhouse-Friderichsen syndrome) as a result of hemorrhage (88, 156) or abscess (155) in the tumor.

Diagnosis

Every patient with paroxysmal or sustained hypertension should have at least one test performed to exclude pheochromocytoma. The most reliable test is the determination of urinary excretion of catechol amines. If this cannot be done, patients who are normotensive when examined may be given histamine, and those who are hypertensive, phentolamine, and the effect on blood pressure determined. A careful history should be obtained of fluctuations in blood pressure, and particular attention paid to patients in whom a rise in blood pressure develops after administration of an anesthetic agent, or a paradoxic rise following a ganglionic blocking drug or sodium amytal (165).

Urinary excretion of catechol amines.—This is the most direct and accurate method of establishing the presence of a functioning

pheochromocytoma, and is supplanting the pharmacologic tests (112). Several technics have been described (12). The catechol amines are absorbed on aluminum oxide (35) or anion exchange resins (168), eluted with acid, and estimated fluorimetrically at various levels of pH following oxidation with potassium ferricyanide (54). A biologic assay is also available, but is less exact (41). The normal daily excretion of catechol amines is about 20 to 40 μg. per 24 hours, but may be considerably increased by trauma, surgical stress, fever, burns, myocardial infarction, and other stress. The catechol amines in normal urine consist predominantly of norepinephrine, with less than 15 per cent being epinephrine, suggesting that its source is mainly the sympathetic nervous system rather than the adrenal medulla. This is further indicated by the normal excretion of catechol amines in Addison's disease.

Catechol amine excretion in 90 per cent of patients with pheochromocytoma is over 300 μg. per 24 hours; the other 10 per cent excrete between 100 and 200 μg., which may be regarded as the lower limit for the diagnosis of a clinically active tumor. Increased urinary excretion is found in most patients with paroxysmal hypertension even during the normotensive period (35). In the occasional patient whose tumor is not actively secreting, the urine may be collected following a provocative injection of histamine. However, 1 patient has been described with normal urinary excretion of catechol amines, even during and after attacks provoked by histamine (90), so that the determination is not infallible. In some instances, reliance must be placed on the clinical diagnosis established by the characteristic attacks occurring spontaneously and in response to histamine, even in the absence of a confirmatory chemical test result.

A tumor releasing both norepinephrine and epinephrine is usually located in one or both of the adrenal glands, while a tumor producing only norepinephrine is usually situated in some other site. The two major urinary metabolites of norepinephrine in patients with pheochromocytoma are normetanephrine and 3-methoxy-4-hydroxy mandilic acid. Assay for these compounds may prove to be an improved means of diagnosis (141).

Blood level of catechol amines.—The catechol amines excreted in the urine represent only 0.3 to 4 per cent of that released by the tumor (54), so that determination of their level in the blood should provide a more sensitive index of hormone production. The blood level has been found to be between 14 and 90 μg. per liter (normal, less than 1 μg. per liter), particularly during attacks (35). Finding rapidly changing blood levels may also be helpful in diagnosis (125). Furthermore, the

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Urinary excretion of catechol amines.—This is the most direct and accurate method of establishing the presence of a functioning

essential hypertension. Hence the initial test is carried out with phentolamine, even though this drug is more likely to produce a false positive response. Patients who have a significant fall in pressure are later tested with piperoxan. When this drug is administered, the effect on urinary flow may also be determined, as it produces an antidiuresis in patients with pheochromocytoma and a diuresis in patients with hypertension due to other causes (89). Serious reactions from phentolamine are more rare than those due to piperoxan, although a fatal fall in blood pressure has been reported (36). A false negative response to either drug may occur, although this too is rare.

Before a test is carried out with histamine, phentolamine, or piperoxan, sedatives and narcotics should be withheld for at least 48 hours, as they may cause false positive results. Antihypertensive drugs should be withheld for at least a week, as they may cause either false positive or false negative results, the former particularly after rauwolfia alkaloids and the latter after 1-hydrazinophthalazine (hydralazine; Apresoline). Dibenamine and its analogues, which block the action of epinephrine and norepinephrine on effector cells, are no longer used in diagnosis because of a high proportion of false positive responses.

ROENTGENOGRAPHY.—Intravenous pyelography reveals displacement of the kidney or other evidence of an overlying mass in only 20 per cent of the patients with pheochromocytoma. The aortogram or perirenal or presacral injection of air or oxygen localizes a tumor in about half the patients, but these procedures entail a small but definite risk. Since the surgeon must still examine both adrenals and the retroperitoneal area to exclude bilateral or multicentric tumors, it is unnecessary to take the risk. Shock and death following aortography in patients with pheochromocytoma, with the postmortem finding of hemorrhage in the tumor, has been reported (91, 134). Radiopaque dyes (e.g., Diodrast, Hypaque) may produce vascular damage when the local concentration exceeds 35 per cent (159), and it is possible that the vasoconstrictor action of norepinephrine may make the tumor and surrounding tissue more susceptible to damage. Rarely, the dyes may cause an allergic reaction and sudden death (118). Perirenal air insufflation may, on rare occasions, produce air embolism or precipitate a severe hypertensive paroxysm. The presacral route is safer, but either procedure not infrequently results in inconclusive or even misleading information. Therefore, insufflation, like aortography, cannot be recommended as a routine procedure. If the clinical evidence and results of chemical and pharmacologic tests indicate the presence of a pheochromocytoma, the next step is laparotomy and bilateral adrenal exploration. The operative procedure would differ only in the rare

site of the tumor can be effectively localized by introducing a radio-paque catheter under fluoroscopic control to obtain blood samples from selected parts of the venous system.

Response to histamine.—When the blood pressure is normal between attacks, 0.05 mg. of histamine base is injected intravenously. After a drop in pressure lasting 30 seconds, the blood pressure rises in patients with pheochromocytoma by more than 60/30 mm. Hg (131). To be significant, the increase in pressure must be more than that produced by immersion of the forearm and hand in ice water for 1 minute (cold pressor test). In 21 patients with pheochromocytoma and normal blood pressure between attacks, the injection of histamine produced an average rise in blood pressure of 104/56 mm., which was 60/20 mm. more than the average rise produced by the cold pressor test (83). The response to histamine must be compared with the response to cold to establish the validity of the test. Nevertheless, an occasional false positive test does occur (74). The mechanism of the response to histamine may be either direct stimulation of the adrenal medulla, or reflex stimulation in response to the transient reduction in pressure. There is evidence that both may occur.

Other hypotensive drugs, such as methacholine (Mecholyl), sometimes ganglionic blocking drugs (e.g., tetraethylammonium chloride) and rarely, sodium amytal evoke a paradoxic pressor response after a transient fall (165). The recommended dose of methacholine (10 to 25 mg. subcutaneously) may produce serious heart block and hypotension unless the patient is first given atropine, which prevents these muscarine-like effects but not the pressor response. A diagnostic test which results in direct stimulation of the adrenal medulla employs a ganglionic stimulating compound, 1-1-dimethyl-4-phenyl piperazonium iodide (DMPP). However, the histamine test remains the most useful one in patients who are normotensive when examined.

Response to phentolamine and piperoxan.—If the patient is more than mildly hypertensive, histamine cannot be administered. In patients with sustained hypertension, measurement is made of the response to intravenous injection of 5 to 10 mg. of phentolamine (Regitine) or 15 to 20 mg. of piperoxan benzodioxane (Benodaine), both of which are believed to block the action of epinephrine and norepinephrine on effector cells. The test is considered positive if the blood pressure decreases more than 35 mm. Hg systolic and 25 mm. diastolic for at least 4 minutes. A slight decrease in pressure in the first 2 minutes after injection with return to the basal level is not a positive result. Piperoxan has the disadvantage of occasionally causing a pressor response, with headache and even encephalopathy, in individuals with

Massive doses (40 mg. per liter) of levarterenol may be required for several days postoperatively to maintain the blood pressure (5), particularly after removal of bilateral pheochromocytomas. High concentrations of this drug are best administered through a polyethylene catheter passed into the inferior vena cava (40). Hydrocortisone is usually given intravenously before and after operation, as insufficiency of adrenal cortical tissue may develop, particularly after removal of bilateral tumors. Furthermore, hydrocortisone (also atropine) may potentiate the pressor action of levophed. Despite these measures, a few patients succumb to hypotension postoperatively (5).

Some hypertension may persist or recur after a pheochromocytoma is removed (53). Only occasionally can the cause be elucidated. The concentration of catechol amines in the urine should be redetermined two weeks after operation. A persistently elevated level suggests that there is either a second primary tumor, or that the original tumor was malignant and had given rise to actively secreting metastases (25). Histologic examination of the primary tumor often does not reveal whether the tumor is benign or malignant. Malignant tumors and metastases may be treated by radiotherapy, but with only temporary effect. Occasionally, persistence or recurrence of hypertension may be due to unilateral renal ischemia resulting from operative damage to the renal vascular pedicle, or to the kidney. Hence, if the blood pressure is elevated postoperatively and catechol amine excretion is normal, intravenous pyelography, differential renal function tests, and aortography are advisable, and, if warranted by these tests, renal arterial reconstruction or nephrectomy should be undertaken (65).

ADRENOCORTICAL HYPERPLASIA OR TUMOR

The three main types of steroid hormones secreted by the adrenal cortex are: *(1)* hydrocortisone and corticosterone, which influence the metabolism of protein, carbohydrates, purines, calcium, and to a lesser extent, salt and water; *(2)* aldosterone, which influences the metabolism of sodium, potassium, and chloride; and *(3)* 11-β-hydroxyandrostenedione and other androgenic hormones. Increased secretion of each of these hormones results in hyperadrenocorticism (Cushing's syndrome), primary hyperaldosteronism, and the adrenogenital syndrome. Some patients show clinical features intermediate between, or with various components of, these syndromes. Hypertension is present in 85 per cent of patients with Cushing's disease, over 90 per cent of patients with primary hyperaldosteronism, and only occasionally in patients with adrenogenital syndrome (33).

patient with a tumor in the posterior mediastinum (115) or bladder (124), associated with persistent or intermittent hypertension and positive test results for pheochromocytoma.

Other laboratory data.—The fasting blood-sugar level is above normal in about half the patients with pheochromocytoma. About one-fourth have reduced glucose tolerance and one-tenth frank diabetes (43). These patients have tumors which secrete appreciable amounts of epinephrine. Approximately 50 per cent of the patients, particularly those with persistent hypertension, have a B.M.R. above +20 per cent (upper limit of normal). The association of hypertension with diabetes mellitus or a hypermetabolic state requires careful testing to exclude pheochromocytoma. Electrocardiographic changes may occur, particularly in the S–T segments and T waves, but are not specific. Arrhythmias may also occur, particularly during paroxysms of hypertension, and have been attributed to the release of epinephrine (136).

Management

When a pheochromocytoma is left in the body, it is usually fatal eventually. Therefore, treatment consists of the complete surgical removal of the tumor or tumors, despite the hazards of operation. Anesthesia may be induced by thiopental sodium followed by nitrous oxide and oxygen and supplemented by succinylcholine (Anectine) for muscular relaxation. Cyclopropane, which increases the likelihood of ventricular arrhythmia in the presence of epinephrine, is avoided. A transverse upper abdominal incision is the approach of choice, as it permits examination of both adrenal glands as well as general abdominal exploration. Both glands should be palpated, and the great vessels in the abdomen as well as the base of the mesentery of the small intestine examined. Frequent blood pressure determinations are carried out during the operative procedure, since the pressure characteristically fluctuates widely. It usually rises sharply with the induction of anesthesia, with further rise as the tumor is palpated and mobilized. After the tumor is removed, the blood pressure may fall precipitously to shock levels, particularly in patients who have had persistent hypertension preoperatively. If the pressure does not fall, the presence of an additional tumor should be suspected. A slow infusion of 5 per cent dextrose is maintained throughout the procedure. Dangerous rises in blood pressure are counteracted by injecting phentolamine in 5 mg. doses as a depressive agent (152), while falls in pressure are counteracted by adding levarterenol (Levophed) to the infusion in a concentration of 4 mg. per liter, or higher if needed.

it is likely that the virilism and hypertension are due to the secretion by the adrenal cortex of a hormone other than cortisone. There is evidence that the virilism occurring in this disease is due to failure of hydroxylation at C-21 resulting in the accumulation of the potentially androgenic substance 17-hydroxyprogesterone, and that the hypertension is due to failure of hydroxylation at C-11, resulting in the accumulation of potent sodium-retaining steroids, such as desoxycorticosterone (33). Whether or not a similar or related defect in steroid synthesis or degradation is responsible for hypertension in Cushing's syndrome is not known.

CLINICAL MANIFESTATIONS.—Cushing's syndrome may occur at any age, but usually begins during adult life, the average age of onset being 31 years (120). It is three times as common in females as in males, and often begins during pregnancy or lactation. The blood level and urinary excretion of hydrocortisone and of 11-oxysteroids normally rise during the last 2 trimesters of pregnancy and in the last month reach values characteristic of Cushing's syndrome. The disease is relatively uncommon in the Negro.

The incidence of the various clinical manifestations has been reviewed by Plotz and associates (120). Obesity is the most common finding (97 per cent), with the characteristic distribution over the face, neck, and trunk giving rise to the characteristic "moon" facies, "buffalo" hump, and truncal obesity, with sparing of the extremities. Pain and tenderness of fatty tissue is uncommon. Hypertension is the second most common finding (85 per cent). It is often severe, with a high diastolic pressure, and may proceed to the accelerated (malignant) phase. Muscular weakness occurs in 80 per cent, and mild degrees of hirsutism, particularly of the face, amenorrhea or oligomenorrhea (or impotence in men), plethoric appearance, and purple striae, each in 70 per cent. Mental symptoms, particularly depression, occur in 60 per cent, purpura or easy bruisability in 60 per cent, poor healing of wounds or unusual failure to localize infections in 40 per cent, polydipsia and polyuria in 30 per cent, decrease in stature, kyphosis, and backache due to softening of vertebrae in 20 per cent, and exophthalmos in about 6 per cent.

Occasionally, Cushing's syndrome may be manifested only by marked atrophy of muscle, skin, and bones, without the other features that are commonly observed (100). In children, sexual precocity and an increase in bone age with premature ossification of the epiphyses usually occur, while hypertension, striae, osteoporosis, and spontaneous fractures are usually absent.

One instance of malignant exophthalmos in a patient with Cush-

Cushing's Syndrome

Pathology and mechanism of hypertension.—It is not clear whether the syndrome is initiated by a pituitary, hypothalamic, or adrenal lesion, but the clinical picture is invariably one of hyperadrenocorticism. Morphologic changes are usually found both in the pituitary and the adrenals (2, 120). Almost all patients with Cushing's syndrome are said to have hyalinization of the basophile cells of the anterior pituitary. In approximately one-third, a basophilic adenoma of the pituitary is found, usually accompanied by hyperplasia of the adrenals, and in a few a chromophobe adenoma. Over one-half have hyperplasia of the adrenals, with or without tumor of the pituitary; about one-sixth have carcinoma of the adrenals (148), and a slightly smaller number unilateral benign tumor of the adrenal with atrophy of the opposite gland. Only about one-tenth have morphologically normal adrenals.

Some 10 per cent of patients with Cushing's syndrome due to adrenal hyperplasia or adenoma are reported to have neoplasms other than those involving the adrenal or pituitary glands, particularly carcinoma of the bronchus (82) or ovary (116), or tumor of the thymus (98), pancreas, or adrenal medulla (medulloblastoma or pheochromocytoma) (21). There is no evidence that any of these associated tumors secrete steroids or cause Cushing's syndrome. It has been suggested that the oversecreting adrenal may promote neoplasia.

Administration of hydrocortisone or cortisone to persons who do not have Cushing's syndrome results in most of the clinical and metabolic features of this syndrome, except that there is usually no hypertension unless renal disease is present. Furthermore, diabetic glucose tolerance curves and temporary diabetes are less common in iatrogenic hyperadrenocorticism. Therefore, it is likely that in Cushing's syndrome the hypertension, and perhaps the reduced glucose tolerance, may be due to the secretion of an adrenocortical hormone other than hydrocortisone or corticosterone. The rare patient in whom hypertension develops in the absence of renal disease following administration of therapeutic doses of cortisone may have a defect in the mechanism of steroid degradation (71), possibly hepatic (49) or adrenal in origin.

In patients with the adrenogenital syndrome due to congenital bilateral adrenal hyperplasia, cortisone therapy ameliorates the virilism as well as the hypertension which is occasionally present, and the urinary excretion of 17-ketosteroids decreases (163). Since the latter indicates successful inhibition of the adrenals as a result of the suppressive action of cortisone on the anterior pituitary output of corticotropin,

duction of these steroids, or of the effect of ACTH on steroid production (44), after administration of 9-α-fluorohydrocortisone or cortisone, which inhibits the output of corticotropin by the anterior pituitary, has the same significance (21, 22). These are similar to the tests of stimulation and suppression of 17-ketosteroid excretion in patients with the adrenogenital syndrome (163). However, mote recent reports have indicated that while these relations are generally true, exceptions occur more frequently than in the adrenogenital syndrome, rendering the tests of slighter diagnostic value. Thus, it has been reported that ACTH may produce an abnormal increase in 17-hydroxycorticosteroid excretion in some obese hirsute women who do not have adrenal hyperplasia, and in some patients with adrenocortical carcinoma (148), and may occasionally fail to produce an increase in patients with adrenocortical hyperplasia (108, 146). Likewise, 9-α-fluorohydrocortisone or cortisone may occasionally suppress steroid production in a patient with adrenocortical carcinoma (148), and may fail to suppress steroid production in a patient with hyperplasia (68). It is therefore difficult to demonstrate or exclude adrenal cortical tumor with any degree of assurance by chemical tests, and it seems best at this time to explore the adrenals of all patients with proven Cushing's syndrome.

Some additional tests have also been proposed. Amphenone B (1,2-bis[p-aminophenyl]-2-methyl-1-propanone dihydrochloride) is reported to depress plasma and urinary levels of 17-hydroxycorticosteroids only in patients with Cushing's syndrome, presumably by a direct action on the adrenal cortex (98). The drug also lowers the blood pressure but the mechanism of this is not clear, as there is some depressant effect on the central nervous system. It has been suggested that Amphenone may be helpful in the diagnosis of Cushing's syndrome. The drug is of no use in differentiating between adrenal hyperplasia and carcinoma, as suppression of steroid may occur in either (148).

Roentgenography.—There is usually generalized osteoporosis, particularly evident in the skull, spine, ribs, pelvis, and, to a lesser extent, in the extremities. Pathologic fractures may occur, with or without pain, in the vertebrae, ribs, and pubic rami. Renal calculi occasionally occur as a result of decalcification and hypercalcemia. Neither bilateral adrenal hyperplasia nor basophilic adenoma of the pituitary can be demonstrated roentgenographically. Adrenal tumor can be demonstrated in only a minority of patients, usually by presacral oxygen insufflation and tomography. Perirenal air insufflation is usually less satisfactory, and intravenous pyelography is only occasionally helpful. The diagnosis of adrenal tumor must usually be made by bilateral adrenal exploration. The apparent demonstration of an adrenal

ing's syndrome has been described (105). While exophthalmos has been produced in experimental animals by the administration of cortisone, it has also been suggested that its occurrence may indicate a primary lesion in the anterior pituitary or hypothalamus.

While Cushing's syndrome may rarely undergo spontaneous remission (117, 171), the disease usually progresses and, in the absence of definitive treatment, about 50 per cent of the patients die within 5 years after onset of symptoms (120). Half the patients are said to succumb to bacterial infection, one-fourth to cardiac failure, and one-eighth to cardiovascular accidents or renal insufficiency. Significant atherosclerosis is found in most cases examined post mortem.

DIAGNOSIS. *Laboratory data.*—Reduced glucose tolerance is present in 94 per cent of patients with Cushing's syndrome, and 15 per cent have glycosuria and diabetes (120). The diabetes is seldom severe, and acidosis is extremely rare. The blood eosinophil count is below 100 per cubic millimeter in 80 per cent. Polycythemia occurs in less than half the patients and is seldom severe. The serum concentration of potassium and chloride is reduced and that of bicarbonate elevated (hypochloremic, hypopotassemic alkalosis) in less than half. The urinary excretion of 17-ketosteroids may be low, normal, or elevated, while that of the 11-oxysteroids and 17-hydroxycorticosteroids is usually, though not always, increased. Urinary excretion of more than 12 mg. of 17-hydroxycorticosteroids a day is suggestive of Cushing's syndrome. It is not possible to distinguish between pituitary or adrenocortical hyperplasia or tumor by estimating any of these steroid fractions in the blood or urine, although high excretion of neutral 17-ketosteroids is somewhat suggestive of a malignant tumor of the adrenal cortex (146). However, changes in excretion of this fraction are slighter and of lesser importance in the diagnosis of Cushing's syndrome than of the adrenogenital syndrome.

The EEG is reported to be abnormal in half the patients with Cushing's syndrome, with changes resembling those seen in patients receiving ACTH or cortisone (120).

Adrenocortical stimulation and suppression tests.—The initial reports indicated that the administration of ACTH, by intravenous infusion for 5 hours or by intramuscular injection of long-acting gel, would produce a greater increase in plasma concentration and urinary excretion of 17-hydroxycorticosteroids in patients with adrenal hyperplasia, under anterior pituitary control, than in normal subjects, patients with pituitary basophilic adenoma (100), or those with adrenal tumor, particularly of the malignant type, secreting without aid of the pituitary (16, 22, 68). Conversely, it was felt that suppressing pro-

cortisone (50), must be continued for the rest of the patient's life. There is an increasing reluctance to leave any adrenal tissue behind, as in half or more of the patients so treated Cushing's syndrome eventually recurs, necessitating reoperation. Many therefore now consider it preferable to remove both adrenals in their entirety, and maintain the patient on hormone replacement therapy. The danger of recurrent disease from hypertrophy of the adrenal segment seems greater than the risk of adequately managed, iatrogenic Addison's disease.

Subtotal or total adrenalectomy results in amelioration of almost all the manifestations of Cushing's syndrome. The hypertension, even when in the malignant phase, disappears in two-thirds of the patients, but in the remainder the blood pressure may remain relatively unchanged even after other signs of Cushing's syndrome have improved (149). The osteoporosis may remain unchanged for many months, but improvement gradually occurs (142).

Malignant tumor of the adrenal cortex is excised, if possible, as this may be followed by temporary improvement, although relapse occurs as metastases grow. Roentgen irradiation of the site of the primary tumor or of the metastases is not particularly effective. Hypophysectomy has no effect on metastatic tumor (81).

Primary Hyperaldosteronism

PATHOLOGY AND MECHANISM OF HYPERTENSION.—Aldosterone is normally excreted in the urine at the rate of 0.8 to 6.8 mg. per 24 hours (average, 3.2) in men and 1.7 to 5.5 mg. per 24 hours (average, 3.8) in women (158). The output of this adrenocortical hormone varies inversely with the intake of sodium, and, to a lesser extent, directly with the intake of potassium (92). It appears to be generally independent of the pituitary and is not influenced by adrenocorticotropic hormone. It disappears from the urine after bilateral adrenalectomy and in patients with Addison's disease. The intravenous infusion of *dl*-aldosterone results in sodium retention and potassium diureses (129). The hormone is over thirty times more potent than desoxycorticosterone in this regard (92, 93). Large doses of aldosterone reduce glucose tolerance, though not as much as does cortisone. The amounts administered do not seem to have any anti-inflammatory action.

Increased urinary excretion of aldosterone has been classified as primary if caused by an abnormality of the adrenal cortex alone and secondary if initiated by an abnormality outside the adrenal and unaccompanied by most of the specific features ascribable to aldosterone. Primary hyperaldosteronism is characterized by hypertension, muscu-

tumor on one side merely suggests that that side should be exposed first; if the tumor is found it is removed and operation on the other side is then not required.

MANAGEMENT.—Roentgen irradiation of the pituitary gland results in improvement in approximately one-third of patients with Cushing's syndrome (1, 120), but this form of treatment is now less used than formerly, and is being replaced by exploration of the adrenal glands and subtotal or total adrenalectomy. Irradiation is more effective in patients with adrenal hyperplasia than in those with tumor (28), but the difficulty of completely excluding the latter, even with the help of adrenal stimulation and suppression tests and special roentgenograms, makes adrenal exploration desirable in all patients with Cushing's syndrome. Some recommend the use of massive irradiation doses to the pituitary and hypothalamus (4,000 r delivered in daily increments of 100 r), implantation of radon seeds into the sella turcica, or electrocoagulation of the pituitary to produce partial destruction (1). However, in more than half the patients so treated there is no remission, and they must undergo adrenalectomy in 3 to 6 months.

In the small number of patients with a unilateral benign adrenal tumor, unilateral adrenalectomy results in amelioration of the disease. Since the opposite adrenal is usually atrophied, presumably due to inhibition of the anterior pituitary by circulating corticosteroids (84), postoperative administration of cortisone and ACTH is necessary for a variable time. In most patients with bilateral adrenal hyperplasia with or without multiple small adenomas, the most effective therapy is total or subtotal resection of the adrenal glands (23, 50). Both adrenals must be examined. If an adrenal tumor is suspected, that gland is exposed first and the tumor, if found, is removed. If an atrophic gland is found, a piece is taken for section, but the rest is left *in situ*. The other adrenal is then explored with the expectation of finding a tumor to be removed. If both glands are found to be normal or hyperplastic, one entire adrenal is removed and nine-tenths of the other, or both may be removed *in toto*. In either event, 200 mg. of cortisone or hydrocortisone are given on each of the 2 days before operation and on the day of operation, and at least 100 mg. a day postoperatively. A liter of isotonic sodium chloride is given intravenously on each of the first 4 postoperative days, supplemented, if necessary, by 5 mg. DCA intramuscularly each day. The dose of cortisone is then gradually reduced. If part of one adrenal has been left *in situ*, the cortisone can be discontinued after 1 to 2 weeks in most, but not all, patients. If both adrenals have been removed *in toto*, a daily maintenance dose of 25 to 50 mg. cortisone, and usually 0.12 to 0.25 mg. 9-α-fluorohydro-

ectomy should be performed. These measures generally result in amelioration of the hypertension and of the other manifestations of the disease.

TOXEMIA OF PREGNANCY

CLINICAL MANIFESTATIONS.—Pre-eclamptic toxemia, which occurs in about 2 per cent of pregnancies, is characterized by the development of hypertension, edema, and/or proteinuria after the twentieth week of pregnancy. This triad also occurs in pregnant women with primary hypertension or pyelonephritis, and these disorders, which are much more common than toxemia, may be mistaken for the latter (39). In eclamptic toxemia, the hypertension becomes more severe, and the manifestations of the accelerated (malignant) phase of hypertension, particularly encephalopathy and convulsions, ensue. Death may result from cerebral hemorrhage, pulmonary edema, or, less often, renal failure (29, 86). In most patients, the hypertension and its manifestations are ameliorated within hours to days after parturition, but in some the hypertension may persist, and may even become worse during the first 24 hours. It seems likely that the reversal of toxemia after parturition is due to loss of the placenta rather than of the fetus.

MECHANISM OF HYPERTENSION.—Toxemia of pregnancy is often superimposed upon antecedent hypertensive disease, and even in patients with no history of elevated blood pressure it may be the first overt manifestation of an underlying hypertensive diathesis which exaggerates the sodium and water retention and vasoconstriction that normally occur during the third trimester. The cause of this, and of toxemia, is not clear. During pregnancy, there is an increase in the blood level and urinary excretion of 17-hydroxycorticosteroids, probably from both placenta and adrenals, but the increase is no greater in patients with toxemia or hypertensive disease accompanied by pregnancy than in normal pregnancy (3). The urinary excretion of sodium-retaining corticoid (aldosterone) is reported to be higher in most patients with eclampsia than in normal pregnancy, but some patients do not appear to have a measurable increase (4, 157).

DIAGNOSIS.—The pregnant woman is examined at frequent intervals to detect the earliest signs of pre-eclamptic toxemia: more edema than is physiologic (weight gain of over 2 pounds a week), hypertension, or proteinuria. An increase in these manifestations, or the appearance of headache, nausea, vomiting, or drowsiness, may presage the development of eclampsia, with papilledema, retinal hemorrhages, oliguria, convulsions, and sometimes renal or left ventricular failure.

MANAGEMENT.—Most cases of pre-eclampsia can be successfully man-

lar weakness, paresthesias, tetany, thirst, polyuria, and usually hypopotassemic, hypochloremic alkalosis (18). In most patients with this disorder, the adrenal cortex contains a benign tumor (18, 32, 38). Less often, there is bilateral adrenal hyperplasia, occasionally a malignant tumor (42), and, rarely, morphologically normal adrenals (18, 69). One patient had carcinoma of the anterior pituitary and many of the manifestations of Cushing's syndrome (30).

Secondary hyperaldosteronism occurs in patients with edema due to heart failure, nephrosis, cirrhosis, and possibly toxemia of pregnancy. Hypertension and the other manifestations of primary aldosteronism are usually absent. The genesis of secondary hyperaldosteronism, and the mechanism of hypertension in the primary disorder, are poorly understood.

Clinical manifestations.—Almost all patients with primary hyperaldosteronism have hypertension, which often progresses rapidly to the accelerated (malignant) stage, with high diastolic pressure and papilledema. The blood pressure can often be reduced by antihypertensive medication, particularly ganglionic blocking agents (69). Periodic attacks of weakness, involving mainly the legs and arms, also occur, and are attributed to the disturbance in potassium metabolism. Less often, there are paresthesias and tetany, with positive Chvostek and Trousseau signs, occurring with normal serum calcium concentration and without hyperventilation (18). There may also be polyuria, thirst, and polydipsia. There is usually no edema, although it may occur (93).

Diagnosis.—Primary hyperaldosteronism is characterized by hypopotassemia, alkalosis, and often intermittent hypernatremia. There is excessive renal loss of potassium, and the hypopotassemia often responds poorly to the administration of large amounts of potassium. Weakness and paresthesias may become manifest when the renal loss of potassium is accentuated by the administration of a diuretic, particularly chlorothiazide, or when supplementary potassium administration is stopped. There is usually persistently alkaline urine, mild proteinuria, and hyposthenuria unresponsive to pitressin. The occurrence of spontaneous hypoglycemia and hypomagnesemia (94), and even of hyponatremia (69), have been described. The urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids is normal, while the blood level and urinary excretion of aldosterone are elevated, usually to several times the upper limit of normal.

Management.—Patients exhibiting the clinical and laboratory manifestations of primary hyperaldosteronism should be subjected to adrenal exploration. If a tumor is found, unilateral adrenalectomy is performed. If no tumor is evident, a total or extensive subtotal adrenal-

the age of 25, or after the age of 50, absence of a family history of the disease, or a sudden increase in severity of primary hypertension at any age, should arouse suspicion of a specific etiologic factor. Most forms of secondary hypertension are amenable to surgical cure, particularly unilateral or occlusive vascular renal disease, coarctation of the aorta, pheochromocytoma, Cushing's syndrome, and primary hyperaldosteronism. The examination of every hypertensive patient must include means of identifying these curable forms of the disease: (1) a careful history and physical examination, with palpation of the femoral pulses and estimation of blood pressure in the legs; (2) roentgenography of the chest and intravenous pyelography; (3) determination of blood sugar level and serum electrolyte concentration; and (4) determination of the blood level or excretion of catechol amines, or the response to histamine or phentolamine administered intravenously. The abrupt onset and rapid progress of hypertensive disease, or a decrease in the size of one kidney, usually necessitates differential renal function tests and aortography to exclude unilateral or occlusive vascular renal disease. Bilateral adrenal exploration is essential in the presence of the manifestations of pheochromocytoma (hypertension, often episodic, and increased excretion of catechol amines), or of Cushing's syndrome (hypertension, truncal obesity, purple striae, hirsutism, weakness, reduced glucose tolerance, and, usually, osteoporosis and increased urinary excretion of 11-oxysteroids and 17-hydroxycorticosteroids), or primary hyperaldosteronism (hypertension, weakness, paresthesias, often tetany and hypopotassemic hypochloremic alkalosis, and increased blood level or urinary excretion of aldosterone). In the management of any form of secondary hypertension, curative measures must be instituted before irreversible renal vascular changes occur, since these may perpetuate the hypertension despite elimination of the original cause.

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aged by salt restriction (1 Gm. a day) and administration of diuretics, particularly chlorothiazide. Antihypertensive drugs are necessary only when the blood pressure is markedly elevated. Drugs such as reserpine (85) and hydrazinophthalazine (80) are preferable to protoveratine, other veratrum alkaloids, and ganglionic blocking agents, which are more likely to reduce cardiac output and renal blood flow (59, 77). The effect of these drugs on placental blood flow is not known, but may possibly be similar to their effect on renal blood flow. Unfortunately, oral preparations of reserpine and hydrazinophthalazine are not sufficiently potent to control severe hypertension. Chlorothiazide potentiates the antihypertensive effect of any of these drugs. Bed rest and sedation are also helpful.

When the blood pressure rises and eclampsia occurs, or is impending, antihypertensive medication is administered parenterally. Reserpine (27), hydrazinophthalazine (127), or magnesium sulfate (17) are preferable, but protoveratine (15, 166) may be used if the milder drugs are unsuccessful. Ganglionic blocking drugs are less useful, not only because of their effect on cardiac output (59), and possibly on placental blood flow, but also because of possible undesirable effects on the fetus. Continuous spinal analgesia by lumbar extradural block has been recommended by some (11). If convulsions occur, magnesium sulfate parenterally is better than anticonvulsant doses of barbiturate, since the latter may depress respiration.

Parturition usually soon causes improvement in toxemia. If the patient is near term, labor may be induced by rupture of the membranes and administration of an oxytoxic drug. If the fetus is less than 30 weeks old, the pregnancy may be continued in order to obtain a more mature infant, provided the toxemia can be controlled; otherwise it may have to be terminated. Onset of eclampsia diminishes the chances of delivery of a living infant. After the convulsions have been controlled for at least 24 hours, the pregnancy is terminated.

With improvement in management of toxemia, the maternal mortality has decreased to about 0.3 per cent, but the fetal mortality has remained high (16 per cent), presumably due to ischemia and placental infarction (47).

SUMMARY

In approximately 20 per cent of patients with elevated blood pressure the hypertension is "secondary" to disease of the kidney (unilateral or bilateral), aorta (coarctation), adrenal medulla (pheochromocytoma) or cortex (Cushing's syndrome or primary hyperaldosteronism), or placenta (toxemia of pregnancy). Onset of hypertension before

the age of 25, or after the age of 50, absence of a family history of the disease, or a sudden increase in severity of primary hypertension at any age, should arouse suspicion of a specific etiologic factor. Most forms of secondary hypertension are amenable to surgical cure, particularly unilateral or occlusive vascular renal disease, coarctation of the aorta, pheochromocytoma, Cushing's syndrome, and primary hyperaldosteronism. The examination of every hypertensive patient must include means of identifying these curable forms of the disease: (1) a careful history and physical examination, with palpation of the femoral pulses and estimation of blood pressure in the legs; (2) roentgenography of the chest and intravenous pyelography; (3) determination of blood sugar level and serum electrolyte concentration; and (4) determination of the blood level or excretion of catechol amines, or the response to histamine or phentolamine administered intravenously. The abrupt onset and rapid progress of hypertensive disease, or a decrease in the size of one kidney, usually necessitates differential renal function tests and aortography to exclude unilateral or occlusive vascular renal disease. Bilateral adrenal exploration is essential in the presence of the manifestations of pheochromocytoma (hypertension, often episodic, and increased excretion of catechol amines), or of Cushing's syndrome (hypertension, truncal obesity, purple striae, hirsutism, weakness, reduced glucose tolerance, and, usually, osteoporosis and increased urinary excretion of 11-oxysteroids and 17-hydroxycorticosteroids), or primary hyperaldosteronism (hypertension, weakness, paresthesias, often tetany and hypopotassemic hypochloremic alkalosis, and increased blood level or urinary excretion of aldosterone). In the management of any form of secondary hypertension, curative measures must be instituted before irreversible renal vascular changes occur, since these may perpetuate the hypertension despite elimination of the original cause.

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Cushing's Syndrome

Experience with Total Adrenalectomy

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SINCE Harvey Cushing's initial description in 1932 (27) of the syndrome that bears his name, it has been frequently reviewed in the literature (2, 12, 23, 76, 101). Although Cushing continued to ascribe the physical changes found in this syndrome to basophilic adenoma formation in the anterior pituitary, Kepler and associates (54, 55) eventually pointed out that neoplasia of the adrenal cortex led to the identical syndrome. We restrict the use of the term "Cushing's syndrome" to the pathology directly related to endogenous, *hypercortisolemia* (greater than normal concentration of cortisol in the plasma). We thus eliminate from consideration iatrogenic Cushing's syndrome, hyperadrenocortical states in which the excess steroid is not cortisol, e.g., virilizing hyperplasia, and clinical states of obesity and hirsutism without hypercortisolemia. We use the term "Cushing's disease" only for that form of the syndrome associated with a clinically evident pituitary tumor. Occasional cases of Cushing's syndrome have previously been noted to be due to neoplastic changes of the adrenal cortex. The literature has traditionally viewed the most frequent cause of this syndrome as "adrenocortical hyperplasia." We believe the use of the term "hyperplasia" to be erroneous and in need of correction. Sufficient experience is now available to permit us to recommend substitution of "hyperfunction" for "hyperplasia," since in reality architectural hyperplasia is not observed in most cases of Cushing's syndrome. The advent of corticosteroids for therapeutic use has permitted enhancement of our understanding of the spontaneously occurring Cushing's syndrome and has led to more radical and effective therapy for this

debilitating illness. It is our intention to review current concepts of etiology, diagnostic measures, and current therapeutic regimens. Particular attention will be paid to a critical evaluation of bilateral total adrenalectomy, the treatment used at The New York Hospital-Cornell Medical College during the period 1951–1959. Of the 44 patients with Cushing's syndrome who have been studied during this period, 23 were treated by total adrenalectomy. We believe the latter group large enough to permit the formulation of opinions regarding an obviously radical therapeutic approach. Credit for the initiation of this study belongs to the late Dr. Ephraim Shorr.

ETIOLOGY

Pituitary basophilism is suggested in most early papers on Cushing's syndrome as the first recognized etiology. The early literature, however, revealed associated adrenal pathology before the postulation of an anterior pituitary lesion in this syndrome (11, 68). Most cases of adrenal lesions recorded before Cushing's classic report were virilizing tumors; however, in retrospect, some of these cases were Cushing's syndrome. It is indeed curious that more emphasis was not placed on the adrenal gland at the time Cushing made his report. Despite his conclusion that the primary defect was basophilic adenoma formation in the anterior pituitary, with the implication of increased secretion of corticotropin, Cushing himself paid considerable attention to the possible role of adrenal secretions in the syndrome. Reiteration of Cushing's concept by others without any new evidence led to general acceptance of his theory of a pituitary origin for the syndrome. The main factors lending credulity to the pituitary theory were: *(1)* the predictability of finding basophilic adenoma in the anterior pituitary of many typical cases; *(2)* Crooke's (25) description of what were thought to be specific histologic changes in the basophilic cells; and *(3)* the fact that a number of patients treated by roentgen ray irradiation of the hypothalamic-pituitary region had a remission. There are defects in this line of reasoning in spite of what at first appears to be good circumstantial support for a pituitary origin of the syndrome. The first two arguments crumbled when it was demonstrated that these architectural changes in the pituitary represent retrogressive phenomena secondary to the increased adrenocortical secretion of glucocorticoids (14), and that postmortem examination of considerable numbers of patients without Cushing's syndrome showed basophilic adenoma in the anterior pituitary (24, 31, 98). Further inconsistencies in Cushing's conclusions are the occurrence of this syndrome in the presence of

pituitary adenoma without basophilic elements and in cases without evidence of any anatomic changes in the pituitary (70). In either of these situations it cannot be said with certainty that the anterior pituitary is of no importance in the etiology of Cushing's syndrome. However, the supposition promulgated by Cushing has been weakened considerably.

As already mentioned, the first cases to be reported were demonstrated to be due to adrenal neoplasia (68) and there were also cases without apparent adrenal architectural changes. Failure to recognize that normal appearing adrenal glands were responsible for this progressive and debilitating disease was responsible for the reluctance to diminish the quantity of steroid secreted by surgical reduction of the volume of adrenal tissue. Surgical intervention was further deterred by the absence of adequate replacement therapy. Appreciation of the abnormally excessive production of adrenocortical steroids in this syndrome evolved as methods for measuring these steroids and their excretory products improved. Soon after the chemists provided the pure adrenocortical products for use in man, iatrogenic Cushing's syndrome was recognized. This observation convinced even the most vociferous adherents of the pituitary theory that the adrenal cortex plays a major, if not primary, role in Cushing's syndrome. In most disease states the satisfactory response to a therapeutic regimen, such as ablation of an organ, suggests a direct cause-and-effect relation. However, curative adrenalectomy has not resulted in universal acceptance of the adrenal origin of Cushing's syndrome. Kepler (54), in a thorough analysis of the arguments for and against the various etiologies, concluded that Cushing's syndrome was indeed a disease of the adrenal cortices.

Jailer and associates (49) explored the controversy about the adrenal or pituitary origin of Cushing's syndrome and concluded that the evidence for a pituitary etiology was more convincing. They also discussed the etiologic theory of excess corticotropin production versus increased pituitary secretion of a "corticotropin-potentiating" substance. The evidence for this additional pituitary factor stems from the work of Reinhardt and co-workers (77), Cater and Stack-Dunne (15), Liddle *et al.* (59), and Jailer and associates (49). There is no certainty that these investigators were all measuring or speaking of the same substance, since different assay technics were employed. From evidence available at present, none of the known pituitary secretory products can substitute for this additional adrenotropic substance. It is generally agreed that this substance is not in itself the ascorbic acid-depleting or the steroidogenic factor. This may explain the failure to find corticotropin on assay in the blood of patients with Cushing's syn-

drome (67, 69). Activity of the usual corticotropin has been measurable only in patients with very high titers, for example, in adrenal insufficiency and in 1 patient with a presumed ACTH-producing pituitary tumor (67). However, it seems unlikely that increased corticotropin would be demonstrated in adrenal hyperfunction. A high concentration of cortisol should inhibit increased secretion unless it is assumed that the corticotropin secretion is autonomous in this condition. Decrease of ACTH secretion during corticoid administration is thought to be the mechanism whereby adrenal steroid production is inhibited (44). It is conceivable that these agents may also directly inhibit the adrenal cortex. Exogenous corticotropin causes a marked response in steroid levels of patients with idiopathic adrenal hyperfunction; this again suggests that the adrenal cortex does not work in an environment of overwhelming corticotropin concentration. Jailer suggests that the occasional remission following irradiation of the pituitary supports the concept that a pituitary factor is responsible for the adrenal hyperfunction, but offers no explanation for the failure of many patients to improve after such treatment. Inadequate irradiation may account for some of the failures, but, a number of patients have not responded despite apparently adequate treatment.

Heinbecker and Pfeiffenberger (41) believe that the sites of initial disturbance leading to Cushing's syndrome reside in the paraventricular nuclei of the hypothalmus. These experimental observations correlate with the rare case of Cushing's syndrome with increased intraventricular pressure and with the few cases of this syndrome which on postmortem examination were found to have degeneration of the paraventricular nuclei (108). They believe that denervation of the posterior pituitary by atrophy of the paraventricular nuclei removes a trophic influence from the basophile cells of the anterior pituitary; maturation of the basophile cells is interfered with while the eosinophile cells become hyperfunctioning. Thus, they suggest that Cushing's syndrome is in reality a consequence of hyperfunctioning eosinophile cells. The basophilic adenoma is explained as an attempt to compensate for decreased basophile cell activity. In experiments in the dog after appropriate brain lesions, some of the laboratory data changed toward that found in hyperadrenocortical states; however, no data were available on cortical steroids. It might be pointed out in defense of their suggestion that the occasional success of pituitary irradiation may be due to the fact that the irradiation is received simultaneously by the hypothalmus. It is most tempting to view the changes in the paraventricular nuclei as one does Crooke's changes in the pituitary,

that is, as retrogressive to primary overactivity of the adrenal cortex (14).

The possibility that neuroendocrine factors may be of importance in Cushing's syndrome should be recognized. The significance of the observation of Schally and associates (79) of a corticotropin-releasing factor from the posterior pituitary and hypothalmus cannot at present be evaluated in the etiology of this syndrome. Haynes (40) has demonstrated *in vitro* that corticotropin is a highly specific activator of adrenocortical phosphorylase, and causes subsequent increase in the concentration of reduced triphosphopyridine nucleotide and augmentation of steroidogenesis. If further work should indicate an inability of this tissue to synthesize cortisol in the absence of corticotropin, it would be necessary to accept the presence of functioning pituitary tissue as mandatory for the hyperfunction of adrenal tissue. The logical suggestion of an adrenal cortex supersensitive to corticotropin is appealing, since it would resolve most if not all conflicting data. We would agree with the likelihood that the pituitary secretes an adrenotropic substance in addition to ACTH. It is also probable that this additional factor is necessary in a "permissive role" for adrenal hyperfunction. We are more inclined to agree with Grumbach and collaborators (36) who suggest that adrenal hyperfunction might be due to primary overproduction of an enzyme system necessary for cortisol production. Work in our laboratory with adrenal slices from the patients in this series points to a pattern of dehydrogenase activity different from that observed in adrenal tissue from normal subjects. We cannot exclude the possibility that adrenal enzymes are altered by chronic increased stimulation of the adrenal tissue by pituitary factors. The beneficial results obtained from therapy aimed at the pituitary or hypothalmus does not militate against the idea that the principal defect resides in adrenal enzyme systems if one also assumes the necessity of pituitary material as an activator of cortical steroidogenesis. A disturbance anywhere in the chain would alter adrenal reactivity.

DIAGNOSIS

The diagnosis of Cushing's syndrome rests on the group of clinical characteristics described and on demonstrable elevation of plasma cortisol. Generally, there is good correlation between levels of excreted metabolites in the urine and of plasma cortisol; however, occasional exceptions make determinations of plasma cortisol level desirable. It should be emphasized that not all features of this syndrome are usu-

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ally found in all patients. In endocrine disease, as in diseases in general, the host response to a given pathogenic stimulus varies considerably. A review of the experiences encountered in our series (Figs. 1 and 2) shows that individual variations in the physical as well as the biochemical changes of this disease are common.

Before cortisol assay was readily available, we made the diagnosis

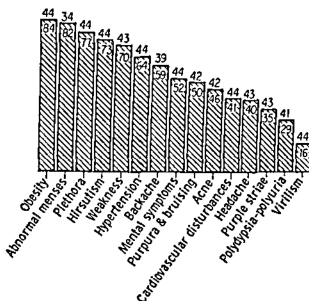


FIG. 1.—Incidence of major signs and symptoms in Cushing's syndrome. Number above each bar represents number of patients evaluated with regard to that sign or symptom; number in each bar, percentage of patients so evaluated in whom that sign or symptom was found.

of Cushing's syndrome in a few patients who did not have laboratory evidence of increased adrenal activity. It is currently recognized that the older technics of assessing adrenal activity were not reliable. Analyses for virilizing adrenal hormones have been available for a longer time, but they were of no particular help in this syndrome since these hormones do not account for the major pathologic changes and are not always elevated. The methods available at present for assay of the adrenocortical steroids permit a more certain evaluation of adrenal function (66, 75, 86). Determination of plasma cortisol is of most value in this syndrome. Urinary corticoids may be affected by a number of metabolic conditions, such as thyroid or liver diseases and obesity (74, 99). The determination of morning and evening plasma cortisol levels may be of particular significance, since it is known that there is marked diurnal variation in normal adrenocortical function (73). In adrenal

hyperfunction, the morning peak may be equalled by the evening plasma cortisol level, while in the normal subject plasma cortisol diminishes considerably in plasma specimens taken in the evening. The corticoid levels fluctuate considerably (9), as is true for many biochemical values determined in disease states. While random specimens may be in the normal range, the mean value of plasma cortisol

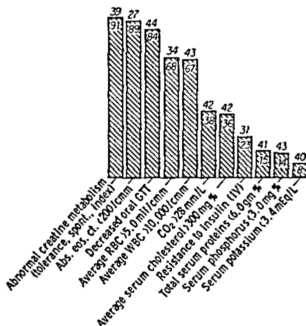


FIG. 2.—Significant preoperative laboratory data in 44 patients with Cushing's syndrome. Number above each bar represents number of patients evaluated with regard to that particular laboratory parameter; number in each bar, percentage of patients so evaluated in whom abnormal values were found.

or urinary corticoids in a patient with this syndrome will generally be in the abnormally high range. Therefore, multiple determinations of corticoids are advised when evaluating adrenal function. A trend has developed to utilize corticotropin stimulation of the adrenals as an aid in establishing the diagnosis of Cushing's syndrome. Corticotropin stimulation tests have been of great value in the diagnosis of adrenal insufficiency, but have been less valuable in the diagnosis of hyperadrenalism. It is questionable whether a diagnosis of Cushing's syndrome may properly be established by virtue of an augmented adrenal response to corticotropin. Like others (65), we have observed persons who show an augmented adrenal response to corticotropin, but who

do not in any other manner suggest a diagnosis of Cushing's syndrome. Currently, there are no available maneuvers which give more reliable information than base-line plasma and urinary corticoid levels. Although we have had few experiences with simultaneous adrenal suppression and stimulation tests, reports in the literature are still too limited to warrant general acceptance of this procedure (19). The failure of corticotropin stimulation to provide conclusive evidence of the type of pathology present has been a serious disappointment (51, 65). Adrenal suppression tests with the new potent steroids have also failed to delineate the pathology in predictable fashion. Malignant neoplastic tissue usually does not respond to stimulation or suppression technics. As a rule, a working diagnosis may be established by repeated evaluation of the base-line day and night plasma steroid values. Extremely high corticosteroid and ketosteroid values generally signify carcinoma of the adrenal cortex, whereas in a patient with only moderately elevated steroid levels, failure to evoke a significant rise in steroids by ACTH administration or suppress them by one of the potent corticoids suggests the presence of adrenal adenoma. However, many exceptions to this pattern have been reported (51, 65), and our experience leads us to concur. Although claims have been made that specific steroids are related to certain types of pathology (25), it is most unlikely that experience with larger numbers of cases will substantiate this observation.

TREATMENT

Medical therapy has been entirely unsuccessful in managing Cushing's syndrome. Testosterone has been used most frequently in an attempt to correct the antianabolic activity of the glucocorticoids (2, 3, 100). The more recent experiences with amphenone have not proved this agent to be of value for *chronic* therapy (63, 93, 103). A *p*-chlorophenyl derivative of dichloroethane has also not proved to be successful, despite good localization in adrenal tissue (83). With further knowledge of steroidogenesis and isolation of the individual enzyme systems, a new approach has been opened in the medical treatment of adrenal disease. Agents have already been developed which inhibit specific enzyme systems shown to be necessary for synthesis of some corticoids (60). It appears most probable that within the next few years medical therapy will be the treatment of choice for idiopathic adrenocortical hyperfunction.

There are many reports on pituitary roentgen therapy (10, 29, 33, 52). Outstanding surveys have been published by Luft (61), Soffer *et al.* (91), Dohan *et al.* (29), and Sosman (92). It must be recognized that

the net results of such therapy depend on two factors which are not under control of the physician: (1) the duration and severity of the disease, and (2) the presence or absence of neoplastic changes in the adrenal tissue—a factor not always looked for in the early days of therapy. There is considerable variation in the dose and manner of irradiation. It is our impression that remission occurs in about 25 to 35 per cent of all patients receiving adequate irradiation. However, it is uncertain how many of these patients have permanent remissions, since cases are usually reported within a relatively short period of time after therapy. It is difficult to find many cases known with a follow-up of 10 or more years. Certain characteristics of roentgen therapy tend to make it desirable to some clinicians. Since it has been fairly well established that normal pituitary tissue is most resistant to usual therapeutic doses of roentgen rays, the assumption that only abnormal pituitary tissue will be affected places this form of therapy in a unique category among therapeutic regimens. Morbidity is admittedly low with this treatment, but other aspects make it less desirable. At least 6 to 8 months must elapse before significant and observable beneficial results may be anticipated. Local skin changes and alopecia are quite common at the portals of entry. Pituitary apoplexy and injury to the optic chiasm are rare but have been observed. Failure to achieve maximum improvement in health despite a general remission has been a common experience. Patients with the 3 most severe aspects of Cushing's syndrome—hypertensive cardiovascular disease, marked psychiatric changes, and advanced bone demineralization—ought not be subjected to the usual delay of 6 months or more before possibly significant benefits from pituitary irradiation become effective. The physician who employs pituitary irradiation today must be as certain as possible that he is not dealing with adrenal neoplasm. As no other method currently available permits absolute differentiation between idiopathic hyperfunction of the adrenal cortex and adrenal neoplasm, surgical exposure of the adrenals is mandatory. We formerly believed that exposure of one adrenal was adequate for judging whether an adrenal neoplasm is present or absent in either gland; however, experience has taught us that unless an adenoma is present in the exposed gland, the gross appearance as well as biopsy and frozen section of that gland may be misleading. It has been our experience that unilateral adrenalectomy frequently gives the patient respite from the disease for 2 to 3 months. Thus, the condition is held in partial control until the possible beneficial effects of pituitary irradiation have accrued.

Many believe that subtotal adrenalectomy is the treatment of choice

for Cushing's syndrome (10, 22, 23, 96, 106). There is agreement that one gland and all but one-tenth of the remaining gland must be removed. Any less radical procedure does not result in cure. The efficacy of subtotal adrenalectomy in curing Cushing's syndrome cannot be estimated accurately because of the impossibility of standardizing the amount of functioning adrenal tissue which will survive surgery. All the studies of the more comprehensive series of subtotal adrenalectomies report considerable morbidity, adrenal insufficiency, and recurrences of disease. Deaths have occurred in the immediate postoperative period as well as months after surgery. Subtotal adrenalectomy has often not improved the complications of this syndrome, notably the cardiovascular difficulties. Skanse *et al.* (88) state that replacement therapy is required by a high percentage of their patients who have had subtotal adrenalectomy. It is also of interest that Kepler (54) reported a high degree of morbidity in the patients at the Mayo Clinic treated with subtotal resection in the precortisone era. This is further evidence that the incidence of adrenal insufficiency in this group of patients is high even in experienced surgical hands. A good correlation exists between cure rate and degree of postoperative adrenal insufficiency, a situation analogous to that of surgery on the hyperplastic thyroid gland for thyrotoxicosis. The more radical the ablation, the more certain the insufficiency, but the more certain the cure. These factors, when considered with the high recurrence rate if too much tissue is left behind, are strong motivation for total adrenalectomy. There is no assurance that a small remnant of adrenal tissue will survive and secrete sufficient hormone for the patient in a period of stress. We think it more sensible to use a procedure with certain cure and associated with little to no increased postoperative morbidity. It may appear paradoxic to treat one disease by intentionally inducing another serious disease. However, the medical management of adrenal insufficiency today is uncomplicated and permits patients to function normally. We have had no deaths and relatively few instances of morbidity from postoperative adrenal insufficiency.

Total adrenalectomy as a therapeutic regimen for diseases other than Cushing's syndrome has been reported by Thorn *et al.* (102), Pearson (71), Bergenstal and co-workers (8), and Hills and associates (43). Kepler *et al.* (55) and Harrison and co-workers (39) were the first to suggest that total adrenalectomy would probably be the operation of choice for Cushing's syndrome, once replacement therapy had been perfected. Reports on the results of total adrenalectomy in the treatment of Cushing's syndrome are still not numerous and in general are limited to small series of patients (1, 6, 35, 39, 80, 89).

AUTHORS' CASE MATERIAL

The series of 44 white patients discussed in detail here includes only well-documented cases of Cushing's syndrome seen at The New York Hospital between 1933 and 1959. All of the patients were studied thoroughly enough to warrant their inclusion in this discussion. Of the total series, 5 died before operation; 3 with carcinoma died shortly after operation; 1 had subtotal removal of a pituitary tumor and roentgen therapy, and 8 years later (1958) repeated excision of the tumor because of recurrence of symptoms; and in 1 patient there was a spontaneous remission. Partial or total ablation of the adrenals was performed in 35, and pituitary surgery in 2; 23 of the group underwent total adrenalectomy.

Clinical Signs and Symptoms

Onset (Fig. 3).—Only those signs and symptoms which could be definitely considered as part of Cushing's syndrome are included in the assessment of the time of onset. This would tend, if anything, to skew the age of onset toward later years.

In 35 patients, onset of the disease occurred in the second, third, or fourth decade. Pregnancy played an important role in the onset. In 10 of the 40 females, the earliest evidence or rapid progress of the syndrome was associated with pregnancy—the first manifestations almost certainly in 4, in another 4 probably during or immediately after pregnancy, definite exacerbation in 1, and probable exacerbation in 1. In retrospect, 1 patient with a pituitary tumor had shown transient evidence of the syndrome, consisting of decreased visual acuity, prob-

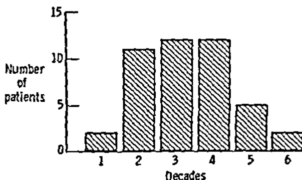


Fig. 3.—Age at onset of signs and symptoms in 44 patients with Cushing's syndrome.

ably decreasing visual fields, and severe headache, in the course of two earlier pregnancies; her third pregnancy was associated with a frank and clinically progressive symptomatology. At least 1 and probably 2 of the 30 women of child-bearing age became pregnant in the active phase of the syndrome. It is also noteworthy that onset of the syndrome in 82 per cent of the women occurred during the potential child-bearing years.

DURATION.—The average duration of symptomatology for the total series was 31 months, for the group with adrenal hyperfunction 28 months. The range was from 10 months to 18 years. The greatest range was in the 29 patients with known adrenal hyperfunction, and least in the 3 patients with proved adrenal carcinoma (10 months to 3 years). However, this may merely reflect the difference in the number of patients in the two categories, as well as the obvious differences in underlying pathology and pathophysiology. No correlation was found between age at onset of symptoms and their duration to time of adrenalectomy or death, nor did there seem to be any sex difference in this factor.

INCIDENCE OF SIGNS AND SYMPTOMS (Fig. 1).—Obesity, which is so marked a characteristic of the syndrome, was present in 37 patients. In many of them it consisted of an abnormal fat distribution rather than a generalized obesity (Plates 1-3). Only 2 of the women were extremely obese, weighing 220 and 230 Kg., respectively. If the 5 patients with minimal abnormal fat distribution and/or obesity are included, 42 of the patients showed this sign. Even in the patients with minimal truncal obesity there was marked abnormal fat deposition about the face (rounding) and in the supraclavicular areas, so that the neck appeared shortened, the normal supraclavicular fossae disappeared, and the ears were relatively obscured in the anterior view.

Menstrual disorders, usually oligomenorrhea or amenorrhea, were present in 28 of 34 women.

Plethora was present in 34 of 44 patients; red cell counts and plethora were not closely correlated, the 2 most plethoric patients having normal counts. Hirsutism was prominent in 34 of 44 patients, more pronounced virilism in 7, and breast atrophy in 3. Weakness, especially of the thighs, which made stair climbing or boarding a bus difficult, was a complaint of 30 of 43 patients. Hypertension, more often mild than severe was found in 28 of 44 patients. Backache, which on the whole correlated well with roentgenographic evidence of bone demineralization, was a complaint of 23 of 39 patients; bone demineralization was found in several who did not complain of backache, while in 3 who did, there was no evidence of demineralization.

Purpura and easy bruising was present in 21 of 42 patients, and purple striae in 15 of 43 patients with a history of this feature. Acneiform eruptions on the face, neck, back, or chest were seen in 19 of 42 patients.

Dyspnea and heart failure were present in 18 of 44 patients, and were usually associated with hypertension. The polydipsia and polyuria in 12 of 41 patients was not directly related to the presence of glycosuria or hypokalemia. Headache of a nonspecific nature was a complaint of 17 out of 43 patients; in 2 patients, it was associated with pituitary tumor.

Intolerance to, or preference for, warm or cold weather was uncommon; a few patients complained of heat intolerance. Poor wound healing was uncommon.

Renal calculi were found in 4 patients; in a fifth, there was a possibility of their presence. Evidence of peptic ulceration was found by history or roentgenography in 2 patients.

In 23 of 44 patients there were clinically significant mental symptoms. The most common were lability of mood, depression, easy crying, and irritability. The symptoms were sufficiently severe in many of the patients to warrant psychiatric consultation and treatment. Several of the patients were considered potentially suicidal.

Significant neurologic signs and symptoms were related to cerebrovascular accidents, except in the 2 patients with pituitary tumor. In the latter, extraocular palsies were present (in 1 before and in 1 after adrenalectomy), as well as bitemporal visual field defects in 1 of them. Widened palpebral fissures were found in several patients, simulating the appearance of exophthalmos.

Preoperative Laboratory Data (Fig. 2)

Hematologic evaluation.—In 25 of 34 patients examined the erythrocyte counts were high, the highest count being 6,500,000 per cubic millimeter. Polycythemia vera was diagnosed in 2 patients before the presence of Cushing's syndrome was recognized.

Average leukocyte counts ranged from 6,200 to 24,700 per cubic millimeter in 43 patients examined, and was over 10,000 in 29 patients.

The average absolute eosinophil count in 24 of 27 patients was below 200, and in 15 of these below 100 per cubic millimeter.

Biochemical evaluation.—The serum sodium concentrations were above 145 mEq. per liter in 10 of 40 patients, and in 2 patients the values were 151 and 156 mEq., respectively. High values were generally associated with increased serum CO_2 levels.

Serum potassium was low in 3 of 40 patients examined, the lowest average value being 2.9 mEq. per liter.

Serum chloride was within normal values in 38 of 39 patients tested. *The results of the Soffer test (90) (DCA and sodium chloride intravenously)* were negative in 3 and positive in 3. In 1 of the 6 patients, the test was done twice; the response was negative the first time and positive the second.

The serum CO_2-combining power was increased in 16 of 42 patients; in 4 the values were greater than 33 mM, and in 10 greater than 30 mM per liter.

The serum calcium levels were normal in 38 of 42 patients. In 2, the values were borderline low (8.7 and 8.8 mg.) and in 2 they were borderline high (11.2 and 11.4 mg.). Of the latter, a 12 year old had a low alkaline phosphatase (2.4 B.U.) and severe bone demineralization demonstrated by roentgenography; the other patient had an alkaline phosphatase value of 5 B.U. and moderately severe bone disease.

Serum phosphorus values were normal in 35 of 42 patients. In 1, it was slightly elevated and was associated with a borderline increase in blood urea nitrogen. In 6, the values were slightly depressed, ranging from 2.6 to 2.9 mg. per 100 ml.; 5 of them had somewhat elevated serum alkaline phosphatase levels, ranging from 5.2 to 8.5 Bodansky units (B.U.); all 6 had normal serum calcium values.

Alkaline phosphatase levels in 4 of 36 adult patients (above the age of 20) were below 2 B.U., and in 11 above 4.5 B.U. Roentgenography failed to reveal bone demineralization in 3 of the patients with low alkaline phosphatase. Correlation between an elevated alkaline phosphatase and *severe* demineralization was poor.

Urinary phosphate depression in response to the intravenous *calcium tolerance test (45)* was normal *in all of the 7 patients tested.*

Serum protein values were within the normal range in 35 of 41 patients; in 6 there was a minimal hypoproteinemia, varying between 5.3 and 5.9 Gm. total protein per 100 ml. No evidence of hyperglobulinemia was found.

Blood urea nitrogen was slightly elevated (22 to 26 mg. per 100 ml.) in 3 patients; 2 of them had congestive heart failure.

Creatine metabolism.—In 31 of 39 patients in whom at least one parameter of creatine metabolism was tested, some abnormality was found. Of 28 patients given a creatine tolerance test (84), 16 retained less than 70 per cent of the administered creatine; the creatine tolerance ranged between 28 and 65 per cent. Spontaneous creatinuria was abnormally high in 20 of the 28 patients (over 100 mg. per 24 hours), and in 6 the creatinuria ranged from *310 to 1,000 mg.* per 24 hours.

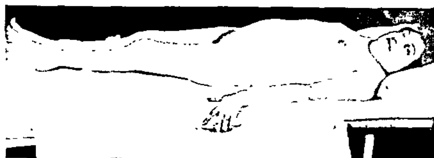




PLATE 1.—Patient with Cushing's syndrome before operation, note typical round face, periorbital puffiness, slight facial acne, and preauricular fat which obscures the ears as seen from the front, head seems to rise directly from shoulders, neck appearing "foreshortened" because of submental and supraclavicular fat; typical pot belly and slender distal extremities, part of the thinness being due to marked muscle atrophy

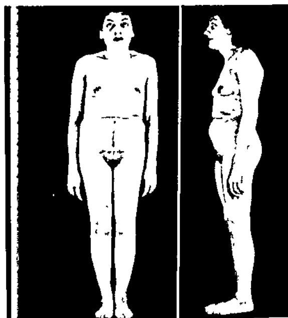






PLATE 2.—Same patient shown in Plate 1, several years after operation; note return of normal distribution of body fat, presence of supraclavicular fossae, slender facies, ears clearly evident, absence of periorbital puffiness, and clear complexion; distal aspects of extremities have regained muscle and fat; dorsal kyphosis, acquired during active phase of syndrome, remains because of vertebral collapse; patient had lost 4 inches in height preoperatively.

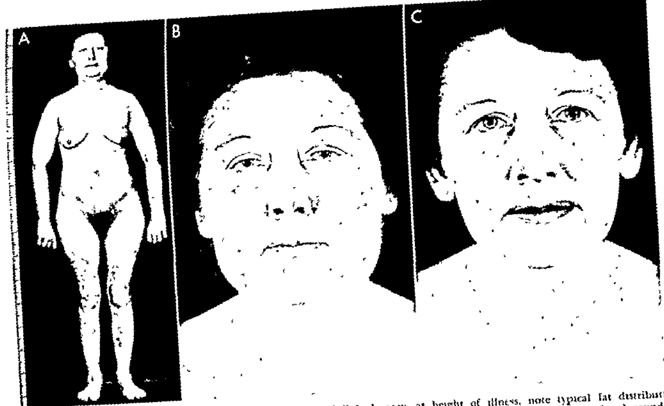


PLATE 3.—Another patient with Cushing's syndrome. *A*, full body view at height of illness, note typical fat distribution, bloated facies, supraclavicular fat pads, and multiple ecchymosis on lower extremities *B*, close up view; note facial rounding, periorbital puffiness, submental and preauricular fat collection, and apparent short neck. *C*, appearance about 4 years after operation.

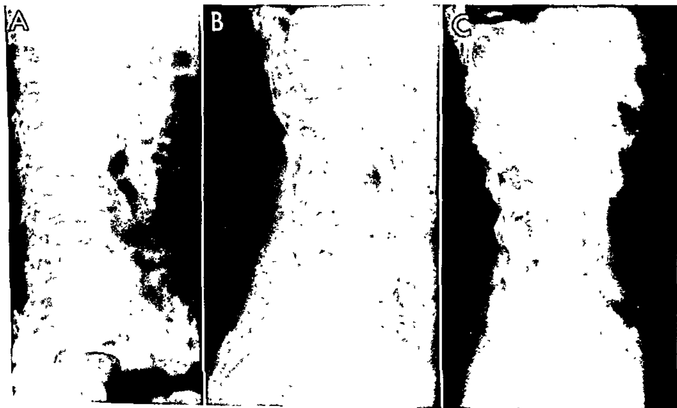


PLATE 4.—Roentgenographic features in Cushing's syndrome. *A*, lateral view of lower thoracic and lumbar spine of 13 year old patient just before operation; note marked, diffuse demineralization, and partial collapse and anterior wedging of several vertebrae. *B*, about 1 year after operation; note increase in mineralization and partial restoration of normal vertebral configuration. *C*, 3 years after operation; note almost normal mineralization and shape of vertebral bodies; areas of lucency still present in centers of vertebral bodies; normal lumbar lordosis has returned.

In general, there was good correlation between pronounced spontaneous creatinuria and clinical symptoms of weakness. The creatinine index (creatinine excreted per day per kilogram body weight) was abnormally low in 12 of the 28 patients. The only abnormality of creatine metabolism in 2 patients was a low creatine tolerance; in 1 of them the creatinine index was also decreased while spontaneous creatinuria was within the normal range.

CARBOHYDRATE METABOLISM.—In 36 patients, tolerance to oral carbohydrate was decreased; in 7, the test result was equivocal; and in 1 patient the result was normal. In contrast, of 31 patients examined, only 23 showed an unequivocally increased insulin resistance in the standard intravenous insulin tolerance test; carbohydrate tolerance was also reduced in all of these patients. On the other hand, 14 of the 36 patients responded normally to the insulin test, and in 7 others the response was equivocal.

THYROID FUNCTION.—The average serum cholesterol level was 150 mg. per 100 ml. or over in 42 patients, and in 15 it was over 300 mg. The protein-bound iodine level was abnormally low in 3 of 16 patients, and normal in 13; clinical hypothyroidism and a clinically evident pituitary tumor were present in 1 of the 3, while in 2 the serum cholesterol levels and B.M.R. were normal, and there was no clinical evidence of hypothyroidism. Uptake of I^{131} at 24 hours was abnormally low in 3 of 6 patients; the lowest value (3 per cent) was found in the patient with a pituitary tumor; in the other 2 (uptakes of 8 and 12 per cent, respectively), values for serum cholesterol and protein-bound iodine were normal, the B.M.R. was -6 and -31 per cent, respectively, and clinical hypothyroidism was not evident.

The average B.M.R. of 6 of 38 patients studied was below -15 per cent, and in 4 it was below -20 per cent; average serum cholesterol levels of 3 of the latter were 253 mg., 303 mg., and 337 mg., respectively.

URINARY STEROIDS AND PLASMA CORTISOL. *Urinary steroids.*—The 24 hour urine samples revealed abnormally high excretion of corticoids in 27 of 29 patients; 15 of the 27 had bilateral adrenal hyperfunction, 8 adrenal adenoma, 2 adrenal carcinoma, and 2 pituitary tumors. In 2 patients with hyperfunction, the corticoid excretion was borderline high. The 2 patients with carcinoma had persistently high excretion values; in one they were consistent with those of hyperfunction or adenoma, while those of the other, who had metastases when first seen, ranged between 44 and 120 mg. per day. In 12 of the patients, the excretion was occasionally normal. Excretion values in bilateral adrenal hyperfunction ranged from 16 to 46 mg., and in adrenal adenoma from 16 to 30 mg., with an average of 26 mg. and 20 mg., respectively.

17-Ketosteroid excretion was definitely increased in 25 of 40 patients, borderline high in 1, and normal in 14. Of the 40 patients, 2 had pituitary tumors, 3 adrenal carcinoma, 6 adrenal adenoma, and 29 adrenal hyperfunction. Excretion was highest in the 3 patients with carcinoma, and high in the 2 with pituitary tumor. Only 2 of the patients with adenoma excreted increased amounts of 17-ketosteroids. Elevated excretion was persistent in 3 patients with adrenal hyperfunction, in 1 with unknown adrenal pathology, and in the patients with adrenal carcinoma; in all the others, excretion was occasionally within the normal range.

Control cortisol levels.—These were determined in 20 patients on fasting blood drawn between 7 and 9 A.M.; 5 had adrenal adenoma, and 15 had bilateral adrenal hyperfunction, 2 with associated pituitary tumor. Fasting levels were definitely increased in 11; in 4 there were borderline elevations; in 5, the results of the few tests performed were equivocal. High or borderline high levels were present persistently in 7.

No significant diurnal variation was found in 2 patients with adrenal hyperfunction.

ACTH stimulation test.—This test (infusion of 40 units of ACTH over an 8 hour period on each of 2 consecutive days) was given to 19 patients: 15 with adrenal hyperfunction, 3 with adrenal adenoma, and 1 with adrenal carcinoma. The plasma cortisol levels rose abnormally high (over 50 μg. per 100 ml.) in 13 patients with adrenal hyperfunction, but "normal" in 1 patient with hyperfunction associated with pituitary tumor, and subnormal in the fifteenth patient. In the 4 patients with adrenal tumor, the results were: 2 patients hyperresponsive to the tests, and no further increase in the high control plasma cortisol level in the patient with adrenal carcinoma.

A repeat ACTH test before the second adrenalectomy in 4 patients gave essentially similar cortisol levels as the first test.

In 4 other patients, the ACTH test produced a two- to fourfold increase in the urinary corticoid values (24 hour specimen) over base-line levels on the first day, and often higher and more variable values on the second day. A two- to fourfold increase in these levels after a single ACTH infusion is normal. The elevated cortisol levels after the first day's infusion of ACTH in patients with adrenal hyperfunction tended to remain above control levels for the next 16 hours.

Suppression test.—For this test, 100 to 150 mg. of cortisol per day was given in divided doses by mouth for 5 days to 3 patients with proved adrenal hyperfunction. Urinary ketosteroid excretion was not decreased. When 6 to 10 mg. of 9α-fluorohydrocortisone was given to

2 patients with adrenal hyperfunction, plasma cortisol and urinary 17-ketosteroid and corticoid levels decreased within 2 days. Dexamethasone (*Δ'-9α-fluoro-16α-methylhydrocortisone*), 2 *mg.* per day orally, suppressed excretion of ketosteroids and corticoids in the patient with a pituitary tumor and proved adrenal hyperfunction. Prednisone, 30 mg. per day orally, rapidly suppressed plasma cortisol and urinary corticoids in 1 patient with adrenal adenoma; no fasting plasma cortisol values were detectable while the patient was on this therapy, but an ACTH test during this time revealed a normal response, i.e., a level of 20 to 50 μg. after infusion.

ELECTROCARDIOGRAPHY.—Changes in the precordial S–T segment, compatible with the diagnosis of coronary artery disease, were found in 7 patients; in 4 patients there were minimal S–T changes over the left precordium; and in 20 patients the ECGs were completely normal.

CALCIUM AND NITROGEN BALANCE.—This was adequately studied by metabolic balance technic in 24 patients. Only 3 of 12 patients studied had negative calcium balances with excessive calcium loss (greater than 200 mg. per day, or greater than 3 mg. per kilogram per day) on a low or 150 mg. calcium diet; 2 had borderline hypercalciuria; 1 had minimal hypercalciuria in the face of a normal negative calcium balance while on a low calcium diet. A significant increase in urinary calcium, associated with a medium (approximately 800 mg. calcium per day) calcium intake was found in 7 of 9 patients; however, only 1 of 4 patients on a high (1,500 mg. calcium per day) diet had frank hypercalciuria (none of the 4 were studied on low or medium diets). Calcium balance tended to shift from negative on a low diet to rather strongly positive on a high diet.

Nitrogen balance studies were obtained on 22 patients. In general, most patients were in positive balance or only in insignificant negative balance with moderate nitrogen intakes (9 to 12 Gm. per day). Nitrogen balance tended to become more negative with lower intakes and more positive with higher intakes. Only 1 patient had a severe (8 Gm. per day) nitrogen deficit; this was evident on a low nitrogen (5 Gm. per day) intake; with increases of dietary nitrogen to about 11 Gm. per day, the balance was within normal limits.

PREOPERATIVE ROENTGENOGRAPHY

SKELETON.—All but 1 of the 44 patients had adequate skeletal roentgenography. Some evidence of bone demineralization was found in 23; in 14, the demineralization was mild to moderate (Plate 4), while in 9 the demineralization was severe and generalized, or mild to mod-

erate with vertebral and/or rib fractures. In many, there was demineralization of the skull, including the vault, the base, and the sella turcica. Some patients had severe demineralization of the extremities; in 1 case this was so severe that during early mobilization after adrenalectomy there was a pathologic fracture of the femur. Severe, generalized osteoporosis and multiple compression fractures of vertebral bodies resulted in myelitis at the fifth thoracic level before adrenalectomy in 1 patient.

Of the 23 patients, 1 was a man, and 2 were adolescent boys; 2 of the women were over the age of 40 and 2 were over 45; of the latter, 1 had had her menopause at the age of 33; the other 3 had had amenorrhea of one to several years' duration. The fourth male in our series was a 9 year old boy, and the roentgenograms showed minimal demineralization.

Perirenal and renal area.—Intravenous pyelography was performed in 31 patients in whom adrenal pathology was subsequently established. In the 6 patients with adrenal adenoma, the pyelograms had not been interpreted as demonstrating or suggesting the presence of an adrenal tumor. In 24 patients, the absence of adrenal neoplasia was later proved; 22 of these pyelograms had been correctly interpreted as normal, the other 2 were considered as suggestive of adrenal tumor. A pyelogram interpreted as normal was obtained in 1 patient with a pituitary tumor; the adrenal glands were not explored.

Renal calculi were found in 4 patients, and possibly in a fifth.

Retrograde pyelography in 3 patients showed a definite suprarenal mass in 2, which subsequently proved to be adrenal tumors; the third patient, whose pyelogram was considered normal, later proved to have idiopathic adrenal hyperfunction.

Perirenal air insufflation in 7 patients definitely demonstrated adrenal pathology in 4 only. Although bilateral visualization was not completely adequate in 2, all 4 were correctly interpreted preoperatively (1 adenoma, 3 without neoplasia).

A large adrenal tumor was diagnosed preoperatively on the basis of a nephrotomogram in 1 patient, but in another patient, who was thought to have a left adrenal tumor on nephrotomography, bilateral nodular hyperplasia was found on laparotomy.

Results of Adrenalectomy

Follow-up of 35 of our patients, 1 with carcinoma, has been long enough to permit evaluation of the results of unilateral or total adrenalectomy. The operative procedures had been: unilateral adrenalectomy in 10 patients, total adrenalectomy in 23, subtotal bilateral in

1. Of the other 10 patients, 2 had adrenal carcinoma and are now dead, 6 others died before operation, 1 had a spontaneous remission, and 1 had only pituitary surgery.

Of the 23 patients with bilateral adrenalectomy, 21 had bilateral hyperfunction; 2 patients had adenomas and were adrenalectomized due to uncertainty regarding the presence of a distinct functioning adenoma at the time of surgery. Of the 10 patients with unilateral adrenalectomy, 6 patients had adrenal adenoma. In 4 patients with apparent bilateral hyperfunction, only unilateral adrenalectomy has so far been performed. The pathology was unknown in 4 of those who died before operation; one had a pituitary tumor and adrenal hyperfunction at autopsy; one had adrenal hyperfunction only.

The general clinical improvement following surgery, measured in terms of regression of the signs, symptoms, and laboratory abnormalities of Cushing's syndrome, was classified as excellent in 18, good in 9, fair in 6, and poor in 2. The last mentioned were obese, hirsute women without preoperative evidence of osteoporosis and slight, if any, rise in blood pressure. Initially, 1 of them had had a unilateral adrenalectomy only for what later proved to be bilateral hyperfunction; she has recently undergone a total adrenalectomy, with good improvement over the 5 month follow-up period to date.

The satisfactory postoperative regression of the clinical and, more slowly, the laboratory abnormalities was particularly gratifying, following, as it did, the usually minimal immediate postoperative morbidity and the infrequency of complications resulting from the temporary or permanent state of adrenal insufficiency. No postoperative deaths have occurred. The usual length of hospitalization was 3 to 4 weeks, and less for those who did not require a two-stage total adrenalectomy. In 1 patient, a pancreatic cyst and draining sinus developed after removal of an adrenal adenoma. This required surgical drainage and debridement, resulting in gradual healing within 4 months. Supportive steroid or ACTH therapy could be discontinued 4 months after operation. Another patient required some supportive steroid therapy because of symptoms of adrenal insufficiency for about a year after removal of an adrenal adenoma. These 2 patients have had excellent and good clinical improvement and, subsequently, uncomplicated courses. Therefore, of 35 cases followed for 6 months or more, only 4 have suffered severely or persistently from hypoadrenalism; 2 are described above, and the other 2 had symptoms ascribed to hypoadrenalism and felt better when given larger than usual replacement dosages of cortisone. This increased dosage could be discontinued after 6 to 12 months. In 22, there has been little or no morbidity related to the operation or to the iatrogenic hypoadrenal state produced. Of this

group, 13 had total adrenalectomy; 1 of these was done as a one-stage total adrenalectomy; 1 had unilateral adrenalectomy for adenoma; 4 had unilateral adrenalectomy for subsequent apparent bilateral hyperfunction; 2 had removal of a pituitary tumor, 1 of whom later required total adrenalectomy; 1 had unilateral adrenalectomy followed by pituitary irradiation for "mild" bilateral hyperfunction; and 1 (a young boy) had a subtotal bilateral adrenalectomy.

Episodes of hypercalcemia have occurred in 3 patients with hyperfunction and total adrenalectomy. In 3 patients with emotional disturbances, there was no change in this regard following surgery (2 total adrenalectomies for hyperfunction and 1 unilateral operation for adenoma); 1 patient (hyperfunction, total adrenalectomy) improved after surgery, and 1 patient not overtly disturbed before operation became severely depressed 1½ years after total adrenalectomy for hyperfunction. No improvement in the preoperative renal disease of 1 patient and the transverse myelitis of another patient was noted after operation. Adrenal insufficiency developed in 1 with subtotal bilateral adrenalectomy, and permanent steroid replacement therapy was required.

CHANGES IN CLINICAL STATUS.—There was a pronounced and nearly immediate change toward normal in the appearance of almost all patients who underwent adrenalectomy for adenoma or hyperfunction.

Obesity.—In 13 of 28 patients with moderate or severe preoperative obesity, there was a moderate or marked decrease in obesity and a striking redistribution of body fat toward the normal pattern; in nearly all, the most pronounced weight reduction occurred in the first year after adrenalectomy. The 2 patients with pituitary tumors became less obese after subtotal removal of the tumors. In 5 patients, the weight loss was slight, but fat redistribution was moderate or marked. A relatively minimal decrease in obesity and in the abnormal fat distribution occurred in 7 patients later than 1 year after operation. In 3 patients, neither the obesity nor the fat distribution decreased significantly, and 2 patients had a mild to moderate weight gain within 2 years after operation.

Hirsutism.—Of 27 patients with preoperative hirsutism, 20 showed marked improvement within 1 year, and their hirsutism almost disappeared or did so entirely. The other 7 were in general the most hirsute of the group; 4 showed some improvement, and 3 a minimal improvement during a follow-up of 3 years.

Menstruation.—In 19 of 24 women with preoperative menstrual disorders, the menses became normal. In the other 5, menstruation remained abnormal: 2 extremely obese women continued to have functional menorrhagia, but 1 of them, who had had a unilateral adrenal-

ectomy, became pregnant several years after operation; 1 patient with functional endometrial hyperplasia and menorrhagia had 2 normal menses, then became amenorrheic as the adrenal carcinoma recurred; 1 patient with a pituitary tumor continued to have amenorrhea; and 1 continued to have abnormal menses, mainly oligomenorrhea. Onset of normal menses occurred in 2 girls within 18 months after total adrenalectomy; they were 13 and 15 years old, respectively, at operation.

Pregnancy.—Within 6 months after total adrenalectomy, 2 women with a history of infertility became pregnant. In 4 other women, 6 pregnancies occurred after total adrenalectomy; 3 of them conceived within 1 year, and 1 had 3 pregnancies. The results of the 6 pregnancies were: 1 spontaneous abortion in the first trimester, 1 premature delivery at 7 months, 1 full-term stillborn infant, and 3 full-term, normal, viable infants.

Blood pressure.—Improvement of varying degree was noted in all 26 patients with preoperative hypertension; 20 had normal blood pressure within 18 months; in most, the pressure was normal by 6 months; a few had normal pressure within a few weeks. In 2 patients who were still hypertensive 18 months after operation, although not as much as preoperatively, the pressure gradually returned to normal in the course of 3 and 4 years, respectively, without benefit of hypertensive drugs. In 1 patient with preoperative severe renal impairment and hypertension, the pressure was increasing at 2 years after operation, after an interim period of decreased but persistent hypertension. In 1 patient whose blood pressure had returned to normal within 6 months, it rose in the third trimester of a pregnancy which began within the first few months after operation; there was no history of previous toxemia. Progressive increase of blood pressure in the first postoperative year did not occur in any patient in this group.

Weakness.—No significant weakness was found 1 year after operation in 21 of 25 patients, and many had improved markedly within the first 3 months. Weakness persisted in 1 patient, despite some regression of other signs and symptoms of the syndrome. There was a pronounced, although incomplete, improvement by the end of the first year in 1 patient whose preoperative weakness had been severe. Minimal, persistent weakness was present in 1 patient 3 years after unilateral adrenalectomy for apparently non-neoplastic bilateral hyperfunction, and in 1 patient 1 year after total adrenalectomy.

Acne.—A marked decrease or complete clearing of the acne 12 to 18 months after operation was found in 17 of 20 patients with moderate preoperative acne; in many, marked improvement was noted within 3 months of operation. Of the 3 other patients in this group, follow-up was inadequate in 2, and in 1 the acne recurred, after a 3

month remission, coincident with metastatic spread of adrenal carcinoma.

Purpura.—Follow-up was adequate (8 months or more) in 13 patients with easy bruising. All have shown complete clearing of this sign by 1 year or earlier.

Mental symptoms.—Of 16 patients with moderate or severe emotional disturbances before operation, 15 had improved by 1 year after operation, but 2 of them regressed soon after improvement. In the first, the regression coincided with recurrence of adrenal carcinoma 3 months after unilateral adrenalectomy. In the second, depression became so severe within 1 year after operation that electroshock therapy was instituted at another hospital; this patient has shown marked improvement and remains fairly well with the help of psychotherapy and ataraxic drugs.

CHANGES IN LABORATORY DATA.—In contrast to the change in clinical status, the biochemical abnormalities only slowly returned toward normal after adrenalectomy.

Hematologic evaluation.—In general, leukocyte counts declined, the decrease paralleling the regression of clinical signs and symptoms. The average for 18 patients during their uncomplicated convalescence and thereafter was 9,100 per cubic millimeter of blood (preoperative average for 44 patients, 12,000).

No striking changes were found in hemoglobin values, hematocrit, and erythrocyte counts, but 2 patients with preoperative polycythemia showed a gradual decrease of red cell counts.

The eosinophil counts in 8 patients tended to be higher than the preoperative levels, but not consistently or strikingly. Counts ranged between 70 and 1,080 per cubic millimeter, with an average of 330.

Biochemical evaluation.—Alkaline phosphatase activity did not rise significantly, nor was there any appreciable difference between the values in osteoporotic and nonosteoporotic patients.

Abnormal creatine metabolism, as judged by decreased creatine tolerance, was still present in 6 of 7 patients tested 1 year after operation. In addition, 3 of them showed an increased spontaneous creatinuria, and 2 a decreased creatinine index. In an eighth patient, in whom unilateral adrenalectomy had been performed for apparent adrenal hyperfunction, the preoperative spontaneous creatinuria persisted.

Carbohydrate metabolism in 10 of 13 patients in the first postoperative year was abnormal, as judged by the oral glucose tolerance test, but at 2 years it was normal in 5 out of 6 tested. In another group of patients tested more than 2 years after operation, 3 out of 4 with previously abnormal glucose tolerance were normal. The only abnormal

response was in a patient who had undergone unilateral adrenalectomy for apparent bilateral hyperfunction and whose clinical response has been poor.

Insulin tolerance was tested in 8 patients 6 months to 3 years after operation. Only 2 of them had shown a slight resistance to insulin preoperatively, and in both of them a normal tolerance was found after operation. In 2 other patients who had undergone unilateral adrenalectomy for adenoma, insulin sensitivity was increased.

Serum cholesterol levels rose immediately after operation, but within 1 to 2 years gradually fell to levels lower than the preoperative ones in most patients.

ELECTROCARDIOGRAPHY.—This was done in 8 patients. Of 2 patients whose ECGs before operation had been abnormal, the postoperative ECG was normal in 1, and unchanged in 1. No change was found in the 6 patients with minimal preoperative S–T segment changes or normal ECGs.

CALCIUM AND NITROGEN BALANCE.—Positive calcium balance decreased in 2 patients, and remained unchanged in 2 others. In 3 of 4 patients, nitrogen balance tended to become more positive postoperatively.

Hypercalcemia appeared several weeks to several months after operation in 3 patients. It was associated with hypercalciuria and hyperphosphatemia without azotemia. All had nausea, anorexia, and constipation. Increased cortisone dosage did not relieve the symptoms or depress the hypercalciuria in 2 of them. Estrogen therapy in 1 patient abolished all abnormal biochemical defects within 3 days.

SKELETAL CHANGES.—Of 6 patients with preoperative bone demineralization, 4 adults (31 to 38 years old at operation) showed no significant change in bone density 1 to 6 years after operation, but in 2 girls (both 12 years old at operation) with severe generalized osteoporosis there was marked bone healing and only minimal evidence of diffuse generalized osteoporosis (Plate 4). Their vertebral bodies showed relative central demineralization and dense, apparently new bone formation in the peripheral areas of the vertebrae. Of the 4 adult patients, 2 had adrenal hyperfunction and 2 benign adrenal adenoma; the 2 young girls had diffuse bilateral hyperfunction.

PATHOLOGY

Total adrenal weight was available for 18 patients. In 2 patients the weight of both adrenals was less than 10 Gm., and in 4 patients less than 15 Gm. Combined adrenal weights were between 15 and 20 Gm.

in 6 patients, and 6 additional patients had adrenal tissue weighing between 20 and 30 Gm. The range of weights for normal adrenal glands varies from 2.5 to 12.5 Gm. per gland depending on the textbook of anatomy consulted. Our experience with "normal" adrenals removed from patients with breast carcinoma confirmed this wide range of weights. There is no information available on the ratio of

Adrenal Pathology in 44 Patients with Cushing's Syndrome

Pathology	Number of Patients
Idiopathic hyperfunction (including hyperplasia)[a]	29
Adenoma	6
Carcinoma	3
Unknown[b]	6

[a] Clinically evident pituitary tumors in 2 patients.
[b] No surgical exploration of adrenal area or postmortem examination.

adrenal weight to total body weight. Average dimensions for normal adrenals are 5 × 3 × 1 cm. Most of the adrenals removed from our patients with Cushing's syndrome did not vary greatly from these dimensions. Apparently, therefore, Cushing's syndrome may exist in the presence of combined adrenal weight no greater than that found in normal persons. Our experience contrasts with that of Cope and Raker (23), who state that the adrenal cortex is enlarged in every case of Cushing's syndrome. Unfortunately, the pathologist cannot state unequivocally that adrenal hyperplasia is present. There are no good criteria for a diagnosis of hyperplasia on histologic grounds. Ashworth and Garvey (5) claimed that the adrenal cortices from 4 cases of Cushing's syndrome were characterized by relatively atrophic zona glomerulosa and dense zona fasciculata. A review of our adrenal specimens does not lead us to a similar conclusion. The gross appearance of the adrenal gland is of little help unless an obvious neoplastic condition is present. A frequent finding has been nodularity of the cortical tissue. Since adrenals removed from patients without hyperadrenocorticism show similar structures in the cortex, this too has been of no help. Hamwi and co-workers (38) suggest the possibility that adrenocortical hyperplasia may ultimately lead to adrenocortical carcinoma. Wooley's (107) observations in mice support this suggestion.

We have found that the cortical tissue of patients with Cushing's syndrome reacts differently from normal adrenal tissue when incubated with tetrazolium salts in the presence of an enzyme inhibitor such as fluoride. The glomerulosa of normal adrenal cortex cannot reduce the tetrazolium salts in the presence of fluoride, while that of abnormal

adrenal glands is not inhibited in the same system. Similar observations have been made with adrenal tissue from hypertensive patients (85).

In 3 of our patients, distinct adenomas were found in hyperplastic adrenal tissue. These tumors were larger than the ordinary nodules found in nodular hyperplasia. We believe that there is a difference between this type of adenoma and the neoplastic tumor or adenoma found in association with markedly atrophic cortical tissue. The gland in which the former type of adenoma is found and the contralateral gland are hyperplastic. Generally, a functioning adrenal adenoma is a discreet unit surrounded by a capsule, but attached to atrophic adrenal tissue. The contralateral adrenal is also usually atrophic. This type of pathology was found in 6 of our patients. In 3 patients with adrenal carcinoma, the disease was rapidly progressive.

Relatively little has been reported on the pathologic changes found in the tissues which are involved clinically. A recent report from the Mayo Clinic (82) indicated that of 15 patients with hypertensive cardiovascular disease, 8 had arteriolar changes. A large group, 11 cases out of 17, in contrast to our series, had renal calculi and/or nephrocalcinosis. We have had the opportunity of examining biopsy specimens of skin, bone, muscle, and kidney for histologic changes in almost all of our patients. It was surprising to find that despite clinical evidence suggesting involvement of these organs, little histologic changes were present. The damage appears to be of a biochemical nature not readily assessable by light microscopy. Atrophy of skin and bone were the pathologic diagnosis made most frequently. Most surprising, in the light of the reports of Scholz *et al.* (81) and Kark *et al.* (52), was the relative lack of renal involvement. The latter workers reported a broadening of the glomerular wall with "ribbon-like capillaries" in Cushing's syndrome.

COMMENTS

In our series described here, the ratio of females to males is 10 to 1. It has long been recognized that Cushing's syndrome is significantly more common in the female than in the male (6). The ratio of females to males in the 33 cases reported by Plotz *et al.* (76) is about 4 or 5 to 1. Including the 189 cases they culled from the literature, the over-all ratio of females to males in the total 266 cases is approximately 4 to 1. The age range for the beginning of Cushing's syndrome is extremely wide, since cases have been described beginning in infancy and in the sixth decade. The commonest time of onset is about the age of 30, in our series as well as in those reported by others (6, 76, 91).

The association of Cushing's syndrome with pregnancy and the child-bearing years has been noted (48). It is exemplified in our series by the significant number of patients in whom onset of the disease or its rapid progression occurred in association with pregnancy. In 80 per cent of our female patients onset was during child-bearing years. Abnormal menstruation was the second most common finding on a percentage basis in our series. It should be stressed that infertility is not a constant accompaniment of the abnormal menstruation seen with active Cushing's syndrome. Blatant Cushing's syndrome probably results in relative infertility and a tendency to spontaneous termination of pregnancy. We have seen several instances of conception and normal completion of pregnancy, with delivery of normal full-term infants, during active Cushing's syndrome.

The incidence of signs and symptoms in our series corresponds well with those reported previously (6, 76, 96). Abnormal fat distribution is present in almost 100 per cent. The obesity may be mild, and in a significant number of cases only fat redistribution is evident, without true weight gain. Weakness sufficient to incapacitate the individual at least partly has been observed in most of our patients. In some, the weakness is associated with clinical muscle atrophy; several of our severe cases had rather prominent atrophy of the muscles of the thigh and calf. In 1 patient, a muscle biopsy revealed nonspecific degenerative changes within the muscle fibers associated with lymphocytic infiltration. This finding was thought to be compatible with dermatomyositis, a condition that has been described in association with Cushing's syndrome (16). Little attention has been given to this aspect of Cushing's syndrome in the literature. At operation, thin and friable muscle has been a common finding in our experience. Severe muscle pain and tenderness with clinically advanced muscle atrophy has been observed in 3 of our patients. Polyneuritis has also been found in association with Cushing's syndrome (30, 32). Backache, plethora, and hirsutism were present more or less prominently in two-thirds of our cases. In our experience, hirsutism of a significant degree is not common, and when present is not associated with definite masculinization.

The frequent occurrence of emotional disturbances associated with Cushing's syndrome or administration of corticosteroids has been repeatedly noted (37, 81, 97, 105). ACTH administration does not generally produce the same psychiatric disturbance as that seen in Cushing's syndrome (97). Euphoria is predominant in the former, while patients with Cushing's syndrome most often reveal depression, with anxiety, agitation, and irritability less common. It is difficult to be certain whether these changes are specific results of adrenal hormone imbalance or largely reactions to debilitating disease often associated

with grotesque body changes and loss of sexual appearance and function. Even profoundly disturbed patients may experience marked psychiatric improvement after adrenalectomy, as demonstrated by our own experience and that of others (37). The changes in the secretion of adrenal estrogens and androgens which occur with administration of corticosteroids or in Cushing's syndrome may be important, in some as yet unclear way, in the genesis of the emotional changes seen.

A rise in blood pressure, usually of modest degree, is seen in 2 out of 3 cases in our experience. In many of these instances, cardiac hypertrophy and/or cardiac enlargement are present, corroborating the experience of Scholz and associates (82). Heart failure was observed in some 41 per cent of patients in our series, and was not always associated with elevations in blood pressure. It may be that persistent hypercortisolemia produces depletion of myocardial potassium. Despite some reports to the contrary (20, 95, 100), we have found chemical or electrocardiographic evidence of hypokalemia to be unusual. There is no evidence to date that increased aldosterone secretion occurs in these patients. Adrenal hyperfunction has been incriminated in relation to hypertension (72, 85). However, today few would employ surgical ablation of the adrenal glands as a treatment for essential hypertension. In contrast to results obtained in essential hypertension, it is of importance to note the beneficial effect of adrenalectomy on the hypertension in our patients. Only in patients with severe, long-standing hypertension are the results less than good. In these relatively few instances the poor prognosis is apparently based on the irreversible degenerative changes that have occurred in the blood vessels of the vital organs, such as brain, kidney, and heart (82). Cardiovascular decompensation is the most common cause of death in untreated Cushing's syndrome: 4 of our patients died preoperatively of cardiovascular complications of their disease, including pulmonary emboli, congestive heart failure, and in 1 instance a coronary occlusion. A 37 year old woman died approximately 15 months after total bilateral adrenalectomy. She had been obese for at least 20 years and hypertensive for at least 10 years. Blood pressure levels ranged about 260/140 before her first pregnancy 8 years before her adrenalectomy. At the end of the first postadrenalectomy year, her blood pressure was only slightly elevated, with diastolic levels of 100 mm. Hg. Shortly after this she gave birth to a full-term stillborn infant. There was no observed increase in hypertension during pregnancy. About 3 weeks postpartum, a left-sided paresis occurred, with death ensuing in 2 days. Autopsy revealed evidence of a right middle cerebral artery thrombosis, and myocardial infarction with cardiomegaly, and coronary atherosclerosis.

Overwhelming infection has not been observed in our series as fre-

quently as had been noted by others (76). This may be because Cushing's syndrome has been recognized earlier in a large number of our more recent cases and because of the availability of antibiotics. The debilitating aspects of the disease have thus been less prominent than previously described. We do not mean to say that decreased resistance to infection has not been observed in our series: 2 patients died from overwhelming infection in the preantibiotic era. Postoperatively, we have not seen poor wound healing of significant degree.

The skeleton may be demineralized more rapidly and seriously in this syndrome than in any other metabolic disease. Patients have been observed in our series, and by others, to lose 2 to 5 inches in height before the diagnosis of Cushing's syndrome has been established. Debilitating bone pain and fractures have been the presenting manifestations of some of our patients. Most commonly, the vertebral column is markedly demineralized and many vertebral bodies exhibit compression fractures. A diffuse granular demineralization of the skull, such as seen in hyperparathyroidism, may also be found. No pathognomonic bone changes exist in this condition. Although we have had considerable experience with the osteoporosis associated with both spontaneous and iatrogenic Cushing's syndrome, the pathophysiology underlying the bone changes is not completely understood. There appear to be factors in addition to the classic explanation of excessive nitrogen loss as proposed by Albright (2). Hypercalciuria is observed more commonly than excessive nitrogen loss in spontaneous Cushing's syndrome. In euadrenal patients treated with glucocorticoids for periods up to 1 month, nitrogen loss exceeds calcium loss in our experience. The variation in nitrogen and calcium balance data obtained in studying hypercorticoid patients probably depends to a considerable extent on the duration and severity of their disease. In a discussion of the osteopathology of Cushing's syndrome, Sissons (87) reports no evidence for increased osteoclastic activity. We have uniformly found that patients with Cushing's syndrome handle an intravenous calcium load in a characteristic manner: The urinary calcium, which is elevated to begin with, rises higher than in a normal subject, and the serum phosphate is increased to a greater degree than in control subjects during the calcium load. There is suggestive evidence that the extra calcium and phosphate comes from the surface (exchangeable) bone mineral, but this is not yet proved. A recent report by Skeels (89) illustrated the excellent remineralization in a growing child cured of Cushing's syndrome by total adrenalectomy. Moldawer (64) and Howard (46) express differing points of view on the reversibility of osteoporosis in hyperadrenocorticism. Albright and Reifenstein (3) believed that the

apparent reversibility observed on roentgenography is in fact caused by new bone growth around the old porotic bone. Plate 4 illustrates the improvement seen in a child 3 years after total adrenalectomy for idiopathic adrenal hyperfunction. Central areas of persistent demineralization can be seen within the vertebral bodies, more evident in the thoracic than in the lumbar vertebra. This degree of recognizable remineralization cannot be anticipated in adult patients. Our personal experience reinforces these conclusions. The inherent danger of fracture of these pathologic bones presents a constant challenge to the nursing staff. Despite utmost care by our especially trained and experienced nursing staff, 2 of our patients suffered fractures while under our care. Judicious mobilization and regulated physiotherapy are suggested during recovery from surgery. Immobilization should be avoided if at all possible.

The relation between certain nonadrenal tumors and Cushing's syndrome is obscure. Thorne (104) has reviewed the occurrence of bronchogenic carcinoma and Cushing's syndrome. Hubble (47) has done the same for thymic tumors. There are scattered cases of other primary tumors and Cushing's syndrome, among which are gonadal carcinoma (4, 28) and pancreatic carcinoma (13, 78). Only rarely has acromegaly been reported in association with this syndrome (33, 68). In our series, this combination is represented, on clinical grounds, by 1 and possibly 2 patients.

Abnormal carbohydrate metabolism is almost always present in Cushing's syndrome (*see* Fig. 2). Frank diabetes was evident in only about 10 per cent of our cases, which compares well with a 15 per cent incidence in the group reported by Plotz *et al.* (76). There are a number of differences between the steroid diabetes of Cushing's syndrome and pancreatic diabetes (21, 42). In the former, it is unusual to see frank diabetes, great elevation of the blood sugar, or ketosis. The diabetes of Cushing's syndrome is associated with increased excretion of corticoids, insulin resistance, elevated plasma lactic and pyruvic acid levels, in contrast to the findings in pancreatic diabetes. In our experience, insulin resistance demonstrable by the usual intravenous tolerance test is much less common than decreased glucose tolerance. In all instances, the steroid diabetes of Cushing's syndrome is markedly ameliorated immediately after adrenalectomy. Many, but not all, patients then exhibit the expected insulin sensitivity. We have noted in some patients a persistence of decreased carbohydrate tolerance for some months after surgery. It is not clear why abnormal carbohydrate tolerance should persist following cessation of hypercortisolemia.

Scholz *et al.* (82) noted 11 cases with renal calculi out of his total

17 patients with Cushing's syndrome. This complication was evident in only 4 (perhaps 5) (about 11 per cent) of our patients at some time in the course of their disease. Perhaps a large number of these patients are protected from the known hypercalciuria of Cushing's syndrome by the frequently observed polyuria and polydipsia. The mechanism of the latter is unclear and certainly cannot frequently be explained by glycosuria or hypokalemic nephropathy with isosthenuria.

Increasing diffuse pigmentation similar to that seen in spontaneous Addison's disease is not unusual following bilateral adrenalectomy for Cushing's syndrome. In those patients undergoing unilateral adrenalectomy for an adrenal adenoma the pigmentation observed has in general been less intense than that seen in some patients following bilateral total adrenalectomy. In those patients who did manifest pigmentation after unilateral adrenalectomy, the degree of pigmentation tended to decrease with time. However, in some of these patients, darker pigmentation than was evident preoperatively has persisted. The degree of postoperative pigmentation has not correlated well with sex, age, or racial extraction in our experience. The pigmentation that occurs in some of these patients following adrenalectomy is intriguing and perplexing. Our understanding of the physiology of pigmentation has advanced considerably, primarily as a result of Lerner and Takahashi's (57) work. We have found no satisfactory explanation for this increased pigmentation in patients who are receiving sufficient corticoid replacement to correct the metabolic alterations. Lerner and Takahashi have demonstrated that cortisone and hydrocortisone inhibit production of melanocyte-stimulating hormone (MSH). Conceivably, the dose of corticoid necessary for MSH inhibition after adrenalectomy exceeds the replacement dose commonly employed. Unfortunately, no MSH or ACTH assays have been performed on any of our patients. From the findings reported in patients with Addison's disease, it would be a fair assumption that increased titers of MSH would be present in our group of adrenalectomized patients. In view of the known similarity of amino acid chains in the ACTH and MSH molecules, it is possible that the peripheral degradation of ACTH may result in MSH or MSH-like substances in these adrenalectomized patients. This possibility would seem especially tenable if it can be demonstrated that ACTH levels are elevated in some of our pigmented patients. The relation of norepinephrene to MSH activity is not well established, in view of contradictory results of *in vitro* and *in vivo* studies. Conceivably, the adrenal medulla is of importance here in spite of the many extramedullary sites of origin for catechol amines (34).

Nelson *et al.* (67a, 67b), Salassa *et al.* (78a), and Montgomery *et al.* (64a) have reported the occurrence of pituitary tumors in patients totally or subtotally adrenalectomized for Cushing's syndrome. Although in these cases evidence for a pituitary tumor was absent prior to adrenal ablation, the possibility of a small pituitary tumor being present prior to surgery must be considered. None of these cases had removal of an adrenal adenoma. The average time for development of clinical evidence of the pituitary lesion was 3 years. These patients gradually developed markedly increased skin pigmentation. In a few cases, Nelson *et al.* (67a) demonstrated increased plasma ACTH levels. Cortisol in larger than therapeutic doses failed to significantly reduce plasma ACTH. Evidence for elevated plasma MSH levels is not as convincing. It is conceivable that the increased pigmentation is due solely to the ACTH excess as discussed above. These pituitary tumors may be analogous in their genesis to those produced in mice by Furth (34a). Although we have noted increased skin pigmentation in a number of our patients, we have had only 1 patient develop a postadrenalectomy pituitary tumor. This patient had a normal-appearing sella turcica prior to adrenalectomy. At this stage, information regarding the frequency of this complication is inadequate. The incidence appears to be low. Hypophysectomy as the primary treatment for Cushing's syndrome in the absence of good evidence for a pituitary tumor does not at the present time appear justified. Since Cushing's syndrome affects females in the childbearing age predominantly, hypophysectomy with its concomitant loss of gametogenesis appears unwarranted—unless a pituitary tumor is evident. However, in light of these new findings, adrenalectomized patients should unquestionably be followed with skull films and visual fields at regular intervals.

Despite attempts at preoperative differential diagnosis of adrenal hyperfunction versus adrenal neoplasia, no consistently reliable method is at hand. ACTH stimulation tests, adrenal suppression tests, and refined technics for separation, purification, and assay of blood and urinary steroids have proved helpful and have contributed to the knowledge of adrenal physiology. In regard to suppression tests, Liddle (58), reporting on the use of dexamethasone in a large series of collected cases, found good separation of normal from abnormal adrenal function, including differentiation of neoplasia from idiopathic hyperfunction. However, from the clinical aspect of differential diagnosis of the individual case, these procedures have not been reliable. Roentgenography, including intravenous pyelography, retrograde pyelography, perirenal air insufflation, and nephrotomography, have been of aid in patients with large suprarenal tumors but have not disclosed

small neoplasms. False positive interpretations of shadows observed by these technics have occurred in our series. In addition, the technics are not simple and are to a small degree a potential hazard to the patient. In the past, we have used almost exclusively a two-stage operative approach, except in the patients with an obvious neoplasm of one adrenal. We have used a retroperitoneal surgical approach through the bed of the twelfth rib via a lateral incision, except in 3 patients with severe osteoporosis in whom a transabdominal approach was used to avoid the risk of vertebral body fracture possible in the lateral (kidney) position. The two-stage procedure was adopted because it was considered to give a better operative exposure of the glands and provide less shock or stress than bilateral adrenalectomy. We wished particularly to avoid, in cases of bilateral adrenal hyperfunction, the stormy postoperative phase observed by ourselves and others (23, 56) after removal of an adrenal adenoma. This phase consists of anorexia, nausea, weakness, myalgia, and arthralgia, often associated with depression and anxiety. A similar syndrome has been noted after abrupt withdrawal of corticosteroid therapy. Following adrenalectomy, this syndrome occurs within the first postoperative week and may be a period of considerable morbidity, requiring supportive therapy and constant nursing care. Occasionally in the past, patients have died during this phase (23). The condition may be improved, but not fully relieved, by administration of large (300 to 400 mg.) doses of cortisone. The biochemical abnormalities usually observed in hypoadrenalism (hypoglycemia, hyponatremia, hyperpotassemia, and uremia) are not apparent. Unless associated with vomiting or diarrhea, fluid and electrolyte loss is not prominent. The blood urea nitrogen falls to low levels, and may approach undetectable amounts. This is almost certainly due in part to the decreased protein intake during this period. In addition, the sudden cessation of tissue catabolism, perhaps especially the decrease in protein catabolism, following adrenalectomy may contribute to the lowered blood urea nitrogen. With increased experience in the postoperative management of these patients, we have begun to use a transabdominal approach for bilateral adrenalectomy. Impetus for this procedure arises from the previously discussed inadequacy of presently available chemical or roentgenographic methods used to differentiate neoplasia from hyperfunction. The inability to characterize all but obvious adrenal neoplasms by gross and histologic examination argues for a change in technic. With both adrenals exposed, the total available tissue can be ascertained and absence of neoplasia more easily diagnosed. This transabdominal approach will obviate the necessity for three explorations, which may occur when *nor-*

mal-appearing but hyperfunctioning adrenals exist. In our limited experience with simultaneous bilateral total adrenalectomy we have not observed evidence of the postadrenalectomy syndrome. We would include moderate or severe emotional disturbance, moderate osteoporosis, and persistent diastolic hypertension as the three major reasons for surgical intervention in cases of Cushing's syndrome.

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The Control of Erythropoiesis

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CONTRIBUTIONS FROM a number of laboratories have established beyond reasonable doubt that the dynamic equilibrium of the erythron is controlled by a humoral substance most commonly and appropriately referred to as erythropoietin. Classifying it as a hormone at present is justified because it is a chemical substance that is secreted into the blood by one or more organs and stimulates activities in another organ.

We consider erythropoiesis to be wholly under the control of erythropoietin. It therefore follows that we accept the concept of an extraordinarily sensitive system which operates on a "feed-back principle," and not only monitors and responds to the natural disappearance of red cells but also responds to the internal stresses of the body in health and disease and to changes in the external environment (such as ascent in altitude) as well. The increase or decrease in hormone production with the concomitant fluctuation in red cell production maintains a relatively constant red cell mass. This concept of the normal control of erythropoiesis presupposes that the constituents of the red cell are available but not involved specifically in the regulation of the rate of erythropoiesis, except as essential building blocks.

We will not review the literature in detail, but will limit ourselves to a consideration of those reports which, over the years, became the basis of current concepts, and give promise of leading to an even more exciting phase of the work in the years to come. Because some extensive reviews have already been published, we have chosen to include only a brief historic sketch and to emphasize only those investigations that have contributed (1) to the development of methods for the assay of erythropoietin, (2) to deductions concerning the physiologic control

of erythropoiesis, *(3)* to elucidation of the mechanism of the erythropoietic activity of cobalt ion, *(4)* to observations of the site of formation of erythropoietin, *(5)* to characterization of the chemical nature of the substance, and *(6)* to evaluations of the clinical significance of the hormone in various disease states.

In 1952, Grant and Root (47) summarized the information then available about the control of erythropoiesis. Although, at that time, knowledge was more incomplete than it is today, there was general agreement that the dynamic equilibrium of the erythron represented one of the most efficient homeostatic mechanisms known. Disagreement existed, however, concerning several rather fundamental aspects of the problem. Points of differences arose from interpretations of the mechanism by which stimulation of erythropoiesis occurred in response to anemic anoxia, hypoxic anoxia, and cobalt ion.

The evidence of Carnot and Deflandre (15) in 1906 that a humoral substance *(hémopoïetine)* could stimulate red cell production followed Bert's (6) observation that a polycythemia occurred in persons living at high altitude, and Miescher's (73) suggestion that anoxia of the bone marrow was responsible for stimulation of the production of red blood cells. Despite the attractive thesis of Carnot and Deflandre, which was supported only by scanty experimental data, the concept of the control of erythropoiesis accepted most generally until the past decade remained essentially that of Miescher: erythropoiesis in the bone marrow was controlled by the level of oxygen in the marrow substance. It would be inaccurate to state that the Carnot-Deflandre hypothesis was not confirmed until rather recently, since a number of investigators for the most part supported their original thesis (30, 36). Bonsdorff and Jalavisto (10), in 1948, renamed the humoral substance erythropoietin on the grounds that the substance is involved primarily or exclusively in red cell production. Despite these reports, physiologists and clinicans failed to explore this "new" idea with the vigor and enthusiasm it deserved. Although Carnot and Deflandre's concept was revitalized by the work of Bonsdorff and Jalavisto, it was especially Reissmann's (86) report in 1950 which aroused great interest. He demonstrated that when air of a reduced oxygen tension was supplied to one of a pair of parabiotic animals (rats) while the other was maintained in a normal oxygen atmosphere, erythropoiesis increased in both parabionts. Subsequently, Gordon *et al.* (44), Hodgson and Toha (54), Erslev (26), and others presented evidence that there was a substance in the blood of anemic animals which could increase erythropoiesis in the recipients. Borsook and associates (11) then demonstrated that an active erythropoietic substance(s) could be extracted and con-

centrated from anemic plasma. Stohlman, Rath, and Rose (97), in a clinical experiment, observed essentially the same phenomenon as that reported by Reissmann. They were able to show that in a patient with *regional hypoxia secondary to patent ductus arteriosus and reversal* of flow through the shunt erythroblastic hyperplasia was not confined to the area of regional hypoxia but was also found in bone marrow supplied by blood with a normal saturation of oxygen. Their findings, and data from studies of respiration of bone marrow *in vivo* and *in vitro* (46, 104) proved conclusively that local anoxia in bone marrow was not the primary stimulus of erythropoiesis.

However, no clear and simple explanation emerged from these various studies to clarify our understanding of the dynamic equilibrium of the erythron. It was accepted that there was a humoral substance in the blood of anemic anoxic or hypoxic anoxic animals which stimulates red cell production. But it was not clear whether this humoral substance was active only in response to anemic or hypoxic anoxia or whether it had something to do with the maintenance of erythropoiesis under normal conditions. The erythropoietic effect of cobalt was also unknown. As is so frequently the case, essential information about the importance of an erythropoietic hormone (erythropoietin) appeared in the literature, but so many of the reports were in conflict with others that even a discriminating reader was left with a feeling of confusion. Grant and Root (47), however, stated that although the evidence was incomplete, humoral mediation by hematopoietin or a similar agent seemed to offer the most useful working hypothesis for investigating the mechanism of action of the fundamental erythropoietic stimulus.

It is difficult to understand the indifference displayed toward evidence of the existence of a humoral factor(s) that controls erythropoiesis, but it would appear that the lack of simple, reliable, and reproducible methods of assay was one of the important contributing factors.

METHODS OF ASSAY

In the investigation of an elusive substance such as erythropoietin, which appears in the blood in small quantity (even after maximum stimulation), simple, rapid, quantitative, and reproducible assay methods are desirable to characterize its physiologic importance, explore the site of formation, and determine its chemical nature. However, the ultimate test of the product is its capacity to produce an unequivocal elevation in the hemoglobin, red blood cell values, and the red cell mass in animals and man.

Until 1955, all the methods employed to demonstrate the presence of erythropoietin were based on the method first used by Carnot and Deflandre (15). Red cell, hemoglobin, hematocrit, and reticulocyte values of the assay animal were determined before a series of injections of the plasma being tested. A rise in one or more of these modalities after the injections was interpreted as an indication of the presence of the erythropoiesis-stimulating factor in the donor plasma. Gordon and co-workers (43) added another parameter by including myelograms as well as peripheral counts, and Linman and Bethell (64) calculated the erythroid-myeloid ratio of the marrow cells, comparing it with that of appropriate controls.

There are several practical objections to these methods. Aside from the time required to count the elements in the blood and the error inherent in the results, multiple injections of plasma are required. A large volume of plasma must be available if several animals are to be used to assay each plasma sample. Although newer methods employing radioisotope technics appear to be simpler and permit a more rapid demonstration of smaller amounts of activity, the older ones continue to play an important role in investigations of the nature and action of erythropoietin. If Linman and Bethell (65) are correct in postulating more than one erythropoietin, only one of which stimulates proliferation of erythroblasts without simultaneous increase in synthesis of hemoglobin in the cells, the basic technic of determining increases in the number of red cells and reticulocytes, without concomitant changes in the hemoglobin and hematocrit, would appear to be the most direct one for investigations of this aspect of the problem. Regardless of the ultimate number of separate erythropoietic hormones involved in the dynamic equilibrium of erythropoiesis, it must be recognized that the various assays discussed in this section may not all be reflecting the same features in the production of blood.

In our laboratories, most of the assays of erythropoietin are performed with radioisotopes. We have found, however, that the most sensitive assay depends on the stimulation of a reticulocytic response in the transfusion-induced polycythemic mouse (60). The polycythemic mouse is ideal for bioassay because erythropoietin production is presumably shut off by a "nontoxic" physiologic mechanism. Moreover, when the animal has been at zero erythropoiesis for some days, any appearance of reticulocytes is an unequivocal demonstration of erythropoiesis, thus eliminating the possibility of release of stored reticulocytes. The preparation of these mice is laborious, but appears to be justified in critical experiments because they demonstrate so clearly the presence of very small amounts of erythropoietin in the plasma being tested.

In 1955, we showed that radioiron could be employed simply and conveniently to demonstrate the stimulation of erythropoiesis in normal rats given injections of plasma obtained from anemic rats (81). This followed the observation of Huff *et al.* (57) that incorporation of Fe^{59} could be used to measure the rate of erythropoiesis. After 3 daily injections of 2 ml. each of the "anemic plasma" to each rat in a group of normal animals, a tracer dose of Fe^{59}-ferric citrate was given intravenously. The amount of radioactive iron incorporated into the total erythrocyte mass was determined 20 hours later and expressed as a percentage of the administered dose. The average uptake in the group receiving anemic plasma was found to be 46 per cent, in contrast to 33 per cent obtained when saline or normal plasma was administered. This difference, then, was taken as a measure of the erythropoiesis-stimulating properties of anemic rat plasma. Subsequently, it was reported that suppression of erythropoiesis markedly increased the sensitivity of the assay animals; hypophysectomy (32), transfusion-induced polycythemia (32), and acute starvation (33) have all been found effective in suppressing erythropoiesis. Roentgen irradiation (95) and nitrogen mustard (63), which also depress erythropoiesis in animals, provide other experimental conditions satisfactory for assay for erythropoietin.

Hodgson and co-workers (55) agree with us that it is desirable to avoid enumeration of blood elements as a basis for a routine assay, and they have utilized the rate of plasma iron clearance and turnover in an effort to demonstrate the erythropoiesis-stimulating properties of various plasma preparations. Isotope dilution technics have been employed by Van Dyke, Garcia, and Lawrence (101) to test the erythropoiesis-stimulating properties of certain biologic materials. With Fe^{59}-labeled erythrocytes, they measure the increase in blood volume of assay animals following multiple injections of the material being tested.

An additional observation which may lead to the development of another method of bioassay has been reported by Rambach, Alt, and Cooper (83). They measured the stimulatory action of erythropoietin on the incorporation of P^{32} into the DNA of the spleen and bone marrow of the rat.

Finally, the erythropoiesis-stimulating properties of anemic human plasma (70) and rat plasma (89) have been demonstrated by means of short-term bone marrow cultures. Again, we must emphasize the possibility that each assay method may be an expression of a different phase of the erythropoietic process.

One matter that has given rise to much controversy concerns the method by which plasma is prepared for assay. This is quite distinct from the problem of elucidating the chemical structure of erythro-

poietin. If the erythropoiesis-stimulating activity of a biologic specimen is being assessed, only that manipulation or purification required to concentrate weakly active samples or remove inhibitors, if present, or substances capable of causing nonspecific stimulation is necessary.

Loeschcke and Schwartzer (68) and Bonsdorff and Jalavisto (10) were the first to cross species barriers, assaying human plasma in the rabbit. Borsook and co-workers (11) showed that the boiled extract of plasma obtained from anemic rabbits could be assayed in rats. We have observed some loss of erythropoiesis-stimulating properties from anemic plasma after it has been boiled for 10 minutes (49). Nevertheless, despite losses, boiling of plasma before assay appears to be an established procedure (43, 56, 64, 80, 94). Prompted by the observations of Kenton (62), who found that rats are slow to produce antibody in response to injection of soluble antigen, we have demonstrated recently that human plasma, without any previous treatment, can be assayed in rats (49).

Small animals are preferable to large ones for assay because large animals are more expensive to maintain and must be given proportionately more plasma to elicit a given response. Conversely, however, large animals, including man, are able to supply larger amounts of plasma in which erythropoietin titers can be determined.

Two features of the response to erythropoietin in bioassays should be considered. One is the nature of the dose response and the other is the variability of response. Hodgson and co-workers (56) believe that the response to erythropoietin is a linear function of the logarithm of the dose. Recent investigations in our laboratory, using a preparation from the urine of a patient with aplastic anemia which was assayed in the starved rat, confirm Hodgson's findings (40).

Unfortunately, in all the assay systems we have tried to date, there has been some variability of response. Usually, in the assay of a potent preparation, the results are highly significant. But the individual response of each animal in the experimental group shows greater variability than that seen in saline or plasma controls. Uniformity with regard to age, weight, sex, handling, and duration of starvation must be maintained in order to minimize variability. Even with this care, day-to-day variations in the magnitude of response occur, and for this reason we find it helpful to include a standard positive control for each assay. This is most easily accomplished with cobaltous chloride ($CoCl_2$).

It must be emphasized that none of the numerous assay procedures and their current modifications is as yet completely satisfactory. Methods employing bone marrow culture, though of interest, are obviously too cumbersome, crude, and arduous to be of practical value for rou-

tine assays. We have already commented on reasons why assays based on increases in elements in the peripheral blood or bone marrow are not satisfactory for all types of investigations. It should be added that the long period of time during which multiple injections of the test material must be given is also an undesirable feature of the assay based upon increases in blood volume.

Of the various assay systems that we have tried, stimulating the incorporation of Fe^{59} into the red cells of the acutely starved rat has proved to be superior to all others (33). The animals are maintained easily, the total assay time is short in comparison with the time spent in most other procedures, and the results are as a rule reasonably uniform.

The reticulocyte response in the polycythemic mouse (60) is a somewhat more sensitive indicator, however, and is preferable when demonstrations of low titers of erythropoietin are sufficiently important to justify the effort required to prepare and maintain this animal.

We have found the hypophysectomized rat useful, but the expense of such a preparation and the high incidence of infection and death constitute deterrents. The starved rat is superior to the hypophysectomized rat for demonstrating erythropoietin in whole plasma obtained from anemic human donors (52). It is our belief that roentgen irradiated and nitrogen mustard treated rats are not desirable assay preparations; the agents responsible for lowering the rate of erythropoiesis in these animals themselves have a direct effect upon the hematopoietic system.

Recent data suggest that measurement of the incorporation of P^{32} into the DNA of bone marrow or spleen is a less sensitive means of determining erythropoiesis-stimulating properties than is the incorporation of Fe^{59} into the red cells.

The assay procedure employed is, of course, a matter of individual preference, and to some degree is dictated by the aims of the investigation. None of the assay methods in use at present can be completely quantitative. For example, a unit of erythropoietin has not been generally agreed upon by investigators in this field, although in this laboratory we have arrived at a working definition of such a unit. In our own work, especially on purification of erythropoietin, we have adopted a unit of activity which is equal to that response elicited by the subcutaneous injection of 2.5 μM of $CoCl_2$ per day for 2 days into 30 hour starved, male Sprague-Dawley rats (initial weight, 125–170 Gm.). Labeled iron (Fe^{59} citrate) is injected intravenously 24 hours after the second dose of $CoCl_2$; 16 hours after injection of radioiron, the rat is bled by cardiac puncture, and a 1 ml. sample of blood is

counted in a scintillation counter. The results are expressed as *per cent* of total injected iron incorporated into total red cell mass. Control rats given saline instead of $CoCl_2$ provide a base-line incorporation value which is subtracted from the value given by $CoCl_2$ to yield an increment in *per cent* incorporation equal to 1 unit.

No assay method is sensitive enough to permit demonstration of erythropoietin in normal plasma, or in plasma containing only slightly elevated erythropoietin titers, if the plasma is not concentrated before assay. It must be concluded that the ideal method has yet to be devised, although many different assay technics are available which have contributed to our understanding of the dynamics of erythropoiesis. It should be simple enough to be performed quickly on multiple samples, accurate enough to permit detection of small differences, and sensitive enough to demonstrate consistently and quantitatively the presence of minute amounts of erythropoietin.

DEVELOPMENT OF MODERN CONCEPT OF ERYTHROPOIESIS CONTROL

The work of Bonsdorff and Jalavisto (10), Erslev (27), Gordon *et al.* (43), Grant and Root (46), Reissmann (86), Hodgson *et al.* (55), Borsook *et al.* (11), and others, revived interest in the mechanism of the control of erythropoiesis. In reality, investigation had been confined to the demonstration of erythropoietic activity in plasma or urine obtained from mammals with anemic or hypoxic anoxia. No methods were available that might be used to measure the presence or decrease of the hormone in normal blood, and thus it was possible only to speculate on the role of the hormone in the control of erythropoiesis and maintenance of the equilibrium of the red cell mass.

Berlin, Lawrence, and Elmlinger (4) and Van Dyke *et al.* (102) reported that in rats after hypophysectomy the red cell mass was gradually reduced by 50 per cent over a period of about 60 to 90 days.

Investigations in our laboratory on erythropoiesis in the hypophysectomized rat provided a model that led logically to an understanding of the dynamics of the control of erythropoiesis (32). Within 4 days after hypophysectomy, the number of reticulocytes fell precipitously, reaching a minimum 8 to 21 days after the operation. Assessing the rate of erythropoiesis in these animals by counting the number of reticulocytes (Fig. 1, *B*) or by measuring the incorporation of Fe^{59} into the red cells (Fig. 1, *A*) indicated that an approximately tenfold reduction had been effected by 8 to 14 days. This reduction persisted for several weeks.

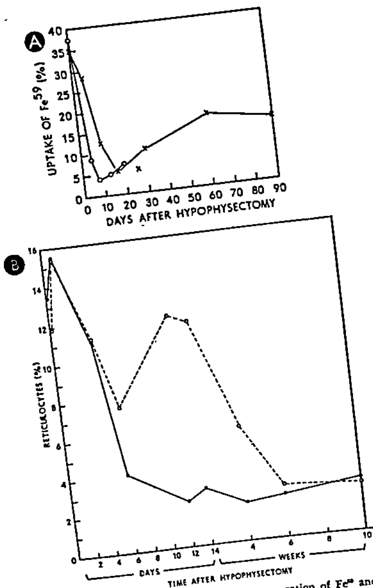


FIG. 1.—Erythropoiesis assessment by red cell incorporation of Fe^{59} and by reticulocyte response in hypophysectomized rats (33). A, red cell incorporation of Fe^{59} by rats hypophysectomized at age of 4 weeks (70–90 Gm.) (—×—) and of 8 weeks (140–160 Gm.) (—o—). B, reticulocyte counts of rats hypophysectomized at age of 4 weeks (—) and of sham-operated rats (- - - -).

These hypophysectomized animals were, at the time of the greatest erythropoietic depression, definitely more sensitive to the injection of a small amount of anemic plasma than normal rats. In an attempt to understand this, we postulated that almost immediately after hypophysectomy, when the normal pituitary hormones are absent, the metabolism of the animal falls more or less abruptly and eventually stabilizes at a level considerably below the normal one. The red cell mass falls slowly because of the reduction in erythropoiesis coupled with the slow rate of destruction of surviving red cells and stabilizes at a level approximately half that of the normal value, a condition that is consistent with the new state of equilibrium. Since the life of the red cell of the rat is about 60 days (5), the reduction in red cell mass within the first 2 weeks after hypophysectomy, even with the drastic reduction in erythropoiesis, is not appreciable.

It was logical to assume that immediately after hypophysectomy, with the over-all reduction in metabolism and before the red cell mass had fallen appreciably, the animal is essentially comparable to a normal animal which had been given too much blood. In teleologic terms, this animal suddenly has more red cells than are needed; the production of erythropoietin therefore ceases and, as a consequence, erythropoiesis stops abruptly. This idea was compatible with our observation that plasma rich in erythropoietin induced active erythropoiesis when it is administered to the hypophysectomized animal. Meineke and Crafts (72) report that oxygen requirement is reduced after hypophysectomy materially strengthens our hypothesis.

We reasoned that if this hypothesis were correct, any experimental procedure which similarly produced a relative or absolute plethora of red cells should bring about a reduction in the production of erythropoietin and consequently a reduction in erythropoiesis. We therefore, studied animals subjected to transfusion-induced polycythemia, acute starvation, and hyperoxia, and found that erythropoiesis was reduced rapidly when these conditions were induced. Elevating the hematocrit of rats or mice from the normal value of 50 to 75 per cent by means of transfusions of homologous washed red cells reduced erythropoiesis almost to zero by 6 to 7 days. Robertson (87) had done this in the rabbit years before. Maintenance of the polycythemic state by repeated red cell transfusions kept the animal almost free of reticulocytes. In fact, by any known method of judging, e.g., the uptake of Fe^{59} by red cells, histologic examination of blood-forming tissues, or reticulocyte counts in the peripheral blood, erythropoiesis had virtually ceased. The polycythemic animals responded to exogenous erythropoietin within 3 to 4 days by an erythroblastic proliferation in the blood-form-

ing tissue, a reticulocytosis, and an increase in the incorporation of Fe^{59} into the red cells.

ACUTE STARVATION.—Animals subjected to starvation have been shown to have decreased basal metabolic rates very shortly after the onset of the fast (75). In acute starvation, a marked decrease in the tissue demand for oxygen occurs without an appreciable change in the number of circulating erythrocytes. Thus, a relative plethora of red

TABLE 1.—RELATION OF OXYGEN SUPPLY AND DEMAND TO ERYTHROPOIESIS (59)

CONDITION	OXYGEN SUPPLY	OXYGEN DEMAND	RATE OF ERYTHROPOIESIS	SENSITIVITY TO ERYTHROPOIETIN
Hypophysectomy	Normal	Decreased	Reduced	Increased
Hyperoxia	Increased	Normal	Reduced	Increased
Starvation	Normal	Decreased	Reduced	Increased
Polycythemia*	Increased	Normal	Reduced	Increased
Anemia due to				
Phlebotomy	Reduced	Normal	Increased	Decreased
Phenylhydrazine	Reduced	Normal	Increased	Decreased
Hypoxic hypoxia	Reduced	Normal	Increased	—
Dinitrophenol administration	Normal	Increased	Increased	Decreased
Triiodothyronine administration	Normal	Increased	Increased	Decreased

* Induced by red cell injection.

cells exists in these animals and, like the other preparations discussed above, a decrease in erythropoietin production and erythropoiesis occurs. Similarly, these acutely starved animals are sensitive to exogenous erythropoietin. Acute caloric deprivation may have a considerable effect on the synthesis of erythropoietin. This possibility still needs clarification. On the other hand, it is known that protein deprivation in rats reduces the incorporation of Fe^{59} into the red cells (7).

HYPEROXIA.—When animals are subjected to an environment of 85 to 95 per cent oxygen, there are small but significant increases in the amount of oxygen carried in the blood (13). It has also been shown that hyperoxia reduces erythropoiesis (98). We subjected rats to an atmosphere of 85 to 95 per cent oxygen and found a decrease in the rate of erythropoiesis and a heightened responsiveness to exogenous erythropoietin (33).

If hypophysectomy abruptly reduced the over-all metabolism of the animal, then the oxygen requirement was also reduced. We thus had an animal in which the oxygen demand was reduced, whereas the oxygen supply was much greater than was needed. Each of the experi-

mental conditions observed demonstrated that the production of erythropoietin was regulated by the relation of oxygen supply to demand rather than to either factor alone (Table 1). This hypothesis is strengthened by the fact that bleeding an animal or producing hemolysis by the administration of phenylhydrazine increases its plasma erythropoietin levels. Under these circumstances, the available oxygen supply is reduced without appreciably affecting the demand. Furthermore, we tested the effect of the metabolic stimulants, dinitrophenol and triiodothyronine, on normal rats and found they caused an increase in the rate of Fe^{59} incorporation into red cells and a decrease in the sensitivity of the rats to exogenous erythropoietin (33).

The metabolic oxygen requirement might be assumed to be fairly stable in a normal organism that is not undergoing unusual stress. With added stress, compensatory mechanisms in the body would become active (increased respiratory rate, cardiac output, etc.) to offset the increased oxygen requirement. If such compensation failed to meet the need quickly, erythropoietin production and erythropoiesis might increase to satisfy the need for increased oxygen. It might also be expected that the production of erythropoietin could occur sporadically, in a sense unnecessarily, in response to temporary breakdowns in respiratory and circulatory mechanisms, which, though brief, might yet be sufficient to trigger the increased production of erythropoietin. With rapid compensation, however, production might fall quickly, and thus the over-all balance of the red cell mass would be essentially unchanged over a long time.

If oxygen demand and supply are involved in this reaction, as they appear to be, then a tissue must be assumed to be present at some site in the body that is sensitive to changes in the partial pressure of oxygen. The stimulus, however, may not involve oxygen directly. It may be some metabolic product which reflects the oxygen demand and supply relation for the body as a whole and which excites production of erythropoietin locally or at a distant site.

EFFECT OF $CoCl_2$ ON ERYTHROPOIETIN PRODUCTION

The long-known effect of cobaltous ion in producing polycythemia in experimental animals and in man was until recently thought to be the result of a direct effect on the marrow (16, 103). In contrast to this idea, we have found that when large amounts of $CoCl_2$ are administered to animals (rats, rabbits, mice, dogs, and sheep) the erythropoietic [illegible] of the plasma rises rapidly (58, 105). This increased plasm[illegible]ietic activity was observed upon assay in starved and

hypophysectomized rats by the Fe^{59} incorporation technic. The small amount of cobalt remaining in the plasma of the animals could not account for the observed erythropoietic effect, although cobaltous ion in larger amounts does stimulate iron incorporation (probably via erythropoietin). The following summary illustrates a representative experiment:

	Fe^{59} INCORPORATED, %			
	HYPOPHYSECTOMIZED		NORMAL	
Saline	2.6	±0.6	26.7	±9.2
Cobalt plasma	19.4	±7.4	35.6	±1.1

While we have not yet proved that the erythropoiesis-stimulating factor in "cobalt plasma" and in "anemic plasma" are identical, we have found their gross chemical properties to be the same, and we hope to complete the comparison of properties in the near future.

The rise in erythropoietin titer of rat plasma after cobalt administration is remarkably rapid, reaching a peak at about 12 hours and declining rapidly thereafter.

Brown and Meineke (12) have shown that an increased erythropoietin titer can be demonstrated in the plasma of rats even after the polycythemia has been established, so long as cobalt ion administration is continued daily.

The mechanism by which cobalt ion produces erythropoietin, and thus increases erythropoiesis, is still obscure. While it seems logical that cobalt might exert its effect by producing an anoxia directly in the sensitive organ which elaborates the hormone, preliminary experiments revealed no effect of cobalt on the respiration of kidney slices *in vitro*.

SITE OF ERYTHROPOIETIN FORMATION

Shortly after their original description of the hormone, Carnot and Deflandre (15) claimed that the marrow was the site where the hormone was formed, since they could demonstrate erythropoietic activity in aqueous extracts of femoral marrow. In their hands, these extracts were as active as serum from anemic animals. They also found appreciable, though inconstant, activity in extracts of brain.

In the last decade, studies by Reissmann (86), Stohlman and coworkers (96), and Schmid and Gilbertsen (91), which firmly established the humoral nature of the stimulation of erythropoiesis by anoxia, have also led to the conclusion that the factor was produced somewhere below the diaphragm. Other studies (28, 65, 97) have shown that a normal bone marrow, or rather, a normally proliferating blood-forming tissue, is not necessary for erythropoietin production.

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creas, or 90 per cent of the liver caused no appreciable inhibition of response, while removal of the kidneys completely abolished it (Table 2).

In an attempt to control the effect of the uremia resulting from bilateral nephrectomy, we have studied the response of rats with ligated ureters. While the resulting uremias, as measured by blood urea nitro-

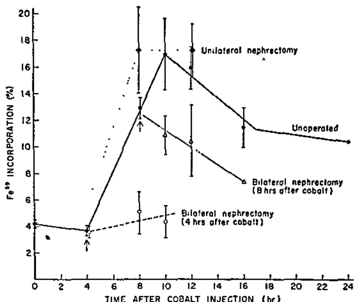


FIG. 2.—Effect of plasma obtained from nephrectomized Sprague-Dawley rats (350 Gm.) stimulated by $CoCl_2$ administration on Fe^{59} incorporation into red cells of starved recipients (61). $CoCl_2$, 75 μM, was injected at zero times, and nephrectomies were done at times indicated by arrows. Enough animals were exsanguinated to provide plasma for assay at each time indicated. Points (•, +, Δ, o) represent averages of 5 assay rats; standard deviations are indicated by vertical lines.

gen, were similar in both the ureter-ligated and the bilaterally nephrectomized animals, the former retained their capacity to respond to cobalt or phlebotomy, while the nephrectomized animals completely lost such responsiveness. When the time between ureter ligation and stimulus is prolonged, the responsiveness does appear to be diminished (41). We feel, however, that this impairment may be due to damage to the kidneys caused by mechanical trauma. At autopsy, the kidneys of ureter-ligated rats were about twice the normal size. The surfaces were pale, and after cutting the kidney perpendicularly to the anteroposterior axis, the cut surfaces were observed to be blanched, especially in the cortical region.

Additional evidence that the kidney is involved intimately in eryth-

Thus, roentgen irradiation and the nitrogen mustards, which reduce the marrow and lymphatic tissue to a reticular stroma as judged by histologic studies, do not impair the capacity of animals to respond to *anemic stimuli by increasing the circulating level of erythropoietin.* Possibly, an endocrine function, or the formation of some substance by reticulum cells of the marrow, may still function unimpaired at a time

TABLE 2.—EFFECT OF PLASMA FROM RATS SUBJECTED TO ORGAN EXCISION FOLLOWED BY $CoCl_2$ STIMULATION ON Fe^{59} INCORPORATION INTO RED CELLS OF STARVED RECIPIENTS (61)

Organ Removed[a]	*Stimulus*	*Fe^{59} Incorporation, %*
None	*None*	3.7 ±0.4[b]
None	$CoCl_2$	14.4 ±1.5
Adrenals and gonads	$CoCl_2$	15.1 ±0.9
90% of liver	$CoCl_2$	12.4 ±0.4
Stomach, intestines, spleen, pancreas	$CoCl_2$	11.7 ±1.2
Kidneys	$CoCl_2$	4.5 ±0.7
None	None	4.8 ±0.6
None	*$CoCl_2$*	16.5[b]
Thymus	$CoCl_2$	16.3 ±1.6

[a] Immediately after organ removal, Sprague-Dawley rats of 350 Gm. weight were given $CoCl_2$, 250 μM per kilogram, subcutaneously; 12 hours later the blood was collected by cardiac puncture. Plasma was assayed in starved rats by standard procedures.
[b] 3 rats.

when the blood-forming tissue appears to be inactive with respect to hematopoiesis. The early observation of Carnot and Deflandre was not confirmed by Gordon, Piliero, and Tannenbaum (44), *who found* no activity in heated extracts of marrow.

The observation that hypophysectomized rats would respond to bleeding by a reticulocytosis (29) and by an increased *titer of erythropoietin* (21, 32) made unlikely the possibility that the pituitary might be involved in the formation of erythropoietin (19). Quite recently, the proponents of the pituitary origin of a specific stimulant *for erythropoiesis have also come to the conclusion* that the pituitary does not supply erythropoietin (100).

Gordon and associates (45) concluded that liver, spleen, *thymus, lung, brain, skeletal muscle, marrow, or red cells* were not the source of erythropoietin, since heated extracts of these tissues derived from anemic animals were devoid of activity. They suggested that either there was no *significant storage in the organ of formation* or that the hormone was produced as an inactive precursor which was activated in the circulatory system.

Jacobson *et al.* (59, 61) *extirpated organs* before studying the response to stimuli, such as $CoCl_2$ or phlebotomy, and found that removal of spleen, stomach, intestines, gonads, adrenals, thymus, pan-

creas, or 90 per cent of the liver caused no appreciable inhibition of response, while removal of the kidneys completely abolished it (Table 2).

In an attempt to control the effect of the uremia resulting from bilateral nephrectomy, we have studied the response of rats with ligated ureters. While the resulting uremias, as measured by blood urea nitro-

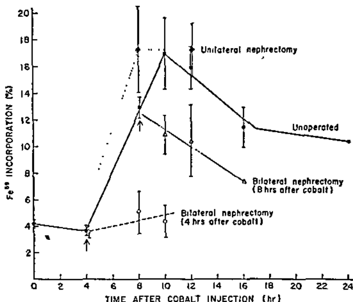


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Additional evidence that the kidney is involved intimately in eryth-

ropoietin formation can be seen in Figure 2. This experiment shows the results of nephrectomy at 4 and 8 hours after $CoCl_2$ administration. It is evident that when the kidneys are removed before an appreciable rise in plasma erythropoietin titer has occurred, there is no subsequent rise in titer. This is also true when the kidneys are removed after the titer has risen, but before it has reached its maximum value (8 hr.).

The rate of disappearance of plasma erythropoietin when the kidneys are excised 8 hours after $CoCl_2$ administration is about the same as in animals whose kidneys are not removed and in which the normal peak titer is reached. The observation that the rates of loss of erythropoietin titer are similar in both seems to indicate that the absence of the kidneys does not cause a toxic reaction which might be responsible for the halt in erythropoietin reproduction.

Some investigators have objected to the conclusion that the kidneys are involved in erythropoiesis. Erslev's (27) data suggests that the uremic state is responsible for the lack of response of nephrectomized animals, since the bilaterally nephrectomized and ureter-ligated rabbits in his study did not show an increase in erythropoietin titer after they had been bled. On the other hand, Mirand and Prentice (74) claim that they found elevated erythropoietin levels in the plasma of rats subjected to hypoxic hypoxia after bilateral nephrectomy or ligation of the ureters. They suggest that perhaps two different erythropoietins were formed in response to different stimuli. Our findings in animals subjected to hypoxic hypoxia (41) fully confirm our earlier observations that animals with ligated ureters retain the capacity to respond to bleeding or $CoCl_2$ by an increased plasma erythropoietin titer about as well as unoperated controls, whereas bilaterally nephrectomized ones do not.

In addition to assaying plasma samples by the technic of Fe^{59} incorporation, we have used the reticulocyte response in polycythemic mice (60) as a means of assay and have obtained quite similar results, i.e., plasma from normal and ureter-ligated animals after stimulation (anemic anoxia and hypoxic anoxia) had high titers; plasma from normal unstimulated animals had none; and plasma from nephrectomized animals subjected to these stimuli had only a questionable titer (Table 3). The finding of any reticulocytes at all in the last group suggests that there may possibly be an extrarenal source of the hormone. There is a factor of about 10 in the difference of the reticulocyte response of the mice given plasma from normal stimulated animals and of those given plasma from nephrectomized stimulated animals. If these responses could be related quantitatively to the amount of erythropoietin

in the plasma samples, we might conclude that an extrarenal source of erythropoietin, if such exists, is a relatively minor one. This would not explain the findings of Mirand and Prentice (74), since they reported that bilaterally nephrectomized rats subjected to hypoxic anoxia attained erythropoietin titers equal to those of normal animals in the same condition.

One obvious desideratum would be the demonstration of erythropoietin in kidney extracts. We have recently been able to show activity in kidney preparations which could not have been due to the presence of plasma in the kidney (39). However, such experiments have not been uniformly successful, and much more definitive evidence is required before the kidney can be accepted unequivocally as the main or sole site of production.

TABLE 3.—EFFECT OF PLASMA FROM VARIOUS GROUPS OF RATS EXPOSED TO SIMULATED ALTITUDE OF 21,500 FEET FOR 8 TO 24 HOURS ON RETICULOCYTE RESPONSE OF MICE WITH TRANSFUSION-INDUCED POLYCYTHEMIA AS COMPARED WITH THAT OF PLASMA FROM NORMAL AND STARVED RATS

Hours at High Altitude	Reticulocytes in Polycythemic Rats, %				
	Normal Rat Plasma*	Nephrectomized Rat Plasma*	Ureter-ligated Rat Plasma*	Starved Rat Plasma*	Saline Treated Rat Plasma*
8	0.9 ±0.33 (9)	0.18 ±0.36 (9)	0.7 ±0.26 (9)	—	—
16	1.71 ±0.49 (7)	0.11 ±0.14 (5)	1.38 ±0.47 (7)	—	—
24	1.78 ±1.47 (8)	0.00 — (8)	1.26 ±0.45 (7)	—	—
0 (not exposed)	0.01 ±0.02 (18)	— —	— —	0.00 (4)	0.00 (18)

* Figures in parentheses, number of animals in each group.

While the resolution of differences both in results and interpretations from the various laboratories awaits further, more decisive experimentation, some indirect evidence concerning the role of the kidney in the elaboration of erythropoietin is worthy of attention. Naets (76, 77) has shown that the rate of erythropoiesis in nephrectomized dogs kept alive by peritoneal dialysis was severely depressed, while in ureter-ligated dogs there was only a minimal depression. Gurney and Pan (49) demonstrated that a group of 7 anemic patients with uremia did not have elevated erythropoietin titers even though they were as anemic as other patients who did have increased amounts of erythropoietin in their plasma. Similar results have been recently reported in 15 of 16 instances in which plasma from uremic patients with anemia was assayed (34).

Osnes (79) reports that in mice massive roentgen irradiation of the kidneys can cause a severe uremia along with anemia. In fact, the

anemia is apparent before the uremia becomes severe. If part of the kidney is shielded from the irradiation, uremia still results but anemia does not appear.

CHEMISTRY

Carnot and Deflandre's (14) observation that the factor in serum was not stable when heated to 56 C. was, until recently, the only information available on the chemical properties of the hormone. Borsook *et al.* (11) found, on the contrary that they could coagulate the greater part of the proteins in anemic plasma by heating it at 100 C. for 15 minutes at *p*H 5.5. Activity was still present in the soluble portion. Unfortunately, they used the term "nonprotein" in the title of their report, while in the text it was made clear that there was some protein in the active fraction. This confusion led to much discussion of the nonprotein nature of erythropoietin, but it has not yet been verified.

Most investigators now agree that the hormone is relatively heat stable in plasma, at least when it is present in the crude state. The loss of hormonal activity on heating seems to be related to the original activity of the plasma. When plasma with a high titer of erythropoietin activity is so treated, detectable activity is retained; on the other hand, heating plasma with a relatively low titer may completely inactivate it, as assayed by current methods.

There is some evidence that proteases inactivate the hormone (58, 69, 94). This might be an indication that the activity is associated with a compound containing several peptide bonds. However, Slaunwhite and co-workers (94) claim that some of the lost activity can be regained if the sample is dialyzed. While it is possible that the activity might be inhibited by products split off by proteolysis of an inactive contaminant, the fact that the assays were done in whole animals would tend to make this unlikely. In our opinion, the most probable interpretation is that the assay method used is not precise enough to permit drawing conclusions from the observed differences between the dialyzed and undialyzed samples.

Reports on the purification and properties of erythropoietin are few. Toha *et al.* (99) have reported that the heat-coagulated proteins of anemic plasma yielded an acetone-soluble fraction with erythropoietic activity and that this fraction could be further purified by chromatography on alumina. This material was assayed by measuring the rate of hemoglobin regeneration in rabbits which had been previously bled. Since this assay procedure is known to give dubious results, the importance of the observations cannot be judged at present. Rambach *et al.* (83), employing paper electrophoresis and studying staining

properties, suggested that an active material prepared from heat-denatured anemic plasma could be classified as an α_2-glycoprotein. Later, they (84) used the anion exchanger, diethylaminoethyl (DEAE) cellulose, for chromatography of active plasma extracts, and they obtained one fraction of high activity. This material was found to be homogeneous by paper electrophoresis at *p*H 8.6. It contained 69.3 per cent protein, 15.6 per cent sialic acid, 7.7 per cent hexose, and 10 per cent glucosamine. While no other preparation has been described in such detail, it is clear that the data of Rambach and co-workers are not extensive enough to permit acceptance of the homogeneity of the material.

Lowy and associates (69) have reported briefly on the partial purification of erythropoietin by ammonium sulfate fractionation and heat denaturation. They gave no details concerning the chemical composition, although they do indicate that sialic acid is present. The active fraction they obtained had four components, as revealed by electrophoresis. All of the activity appeared to be present in the major component. Upon paper electrophoresis, this active material was found to have a mobility between that of albumin and α_1-globulin.

More recently, Rambach *et al.* (85) have indicated that the activity of the preparation was lost after hydrolysis in 0.01N H_2SO_4 at 80 C. for 1 hour. Free sialic acid appeared concomitantly with the loss of activity. Accordingly, they concluded that sialic acid is probably a functional part of the molecule. They also found galactose, mannose, and fucose in their material. Without evidence that there were no gross impurities in their preparation, the assumption that these sugars are located in the biologically active molecule seems to us to be premature.

We have isolated a nonantigenic material from anemic sheep plasma. It is homogeneous by electrophoresis at 3 *p*H values, by ultracentrifugation at 3 *p*H values, and by chromatography on DEAE cellulose, and it contains 83 per cent protein, 6.5 per cent carbohydrate, and 16 per cent sialic acid. Its activity is 1.3 to 5.0 units per milligram of protein, in contrast to an activity of 0.007 units of the original plasma. This "homogeneous" substance, with a molecular weight of 40,000, determined by light scattering, has been further resolved into a large amount of inactive α_1-glycoprotein and a small amount of active hormone with an activity of about 20 to 100 units per milligram. Although we have not yet accumulated enough of the active material to present extensive data on the chemical and physical constitution of the active hormone, we have found that it contains 55 per cent protein, 11 per cent carbohydrate, and 6 per cent sialic acid, and has some of the properties of an α_2-glycoprotein (105).

The partial purification of active materials from urine have also been reported. Van Dyke, Garcia, and Lawrence (101) have concentrated human urine from anemic patients by ultrafiltration, while Winkert and associates (107) have used adsorption on kaolin to separate active material from urine. The most active fraction obtained by the latter had a maximum absorption of ultraviolet at 280 mμ and produced a metachromatic reaction with toluidine blue, indicating a glyco- or mucoprotein.

We have found that the active material in human urine can be adsorbed on benzoic acid or can be obtained by dialysis of the urine before removal of the water by flash evaporation (40).

Hodgson and his group (56) have described the properties of rabbit urinary "hemopoietine." They reported a measurable amount of carbohydrate and considerably more protein.

In a completely different approach to the problem of the chemical nature of erythropoietin, Linman and co-workers (64, 67) have obtained data indicating that an ether-soluble fraction of the heat-stable component of anemic plasma can increase the number of red cells without causing an increase in hemoglobin or in hematocrit levels. They have shown that the results they get with extracts of plasma can also be obtained with synthetic batyl alcohol (α-octadecyl ether of glycerol). However, the amounts of batyl alcohol needed to produce the observed microcytosis far exceed the quantity of the compound that could be present in the amounts of plasma required to give the same effect. The possibility that some analogue of batyl alcohol, much more active on a weight basis, may be a naturally occurring product in the plasma has not yet been the subject of any published report.

From our own experience (105) and that of others (83), we know that a true polycythemia can be produced in experimental animals given completely water-soluble preparations of erythropoietin. This observation tends to cast doubt on the attractive hypothesis of Linman and co-workers.

Gley (37) and Gley and Delor (38) have also suggested that there are two erythropoietic factors: one a protein, called *hémostimuline*, presumably made by the thymus (37); the other, a lipid termed *hématopoïétine* (38). The latter, they claim, is a steroid having one alcohol and three ketone fractions. The activity of the isolated steroid could be duplicated by 11-dehydrocorticosterone and 21-desoxycorticosterone but not by desoxycorticosterone or cortisone. These observations have not yet been confirmed.

Despite the paucity of facts about the properties of pure erythropoietin, we believe that the chemical nature of the hormone will soon be established.

SIGNIFICANCE OF ERYTHROPOIETIN IN MAN



Complete elucidation of the significance of erythropoietin in health and disease, the recognition of which is only now occurring (51, 58, 90), awaits refinement of means of assay.

In early investigations, attempts were made to demonstrate the erythropoiesis-stimulating properties of serum or plasma obtained from subjects at high altitude (68), from newborn babies (cord plasma) (24, 25), and from patients in congestive heart failure. In this regard, the investigations of Bonsdorff and Jalavisto (10) are of particular interest. They sensitized rabbits to human plasma before the rabbits were to be used for bioassay of such plasma. Nonsensitized animals did not respond to the stimulating action of the material. For this reason, their results are difficult to interpret.

Reissmann's (86) observation on parabionts was confirmed by Stohlman, Rath, and Rose (97) in a study of a patient with long-standing patent ductus arteriosus. They found that the stimulation of erythropoiesis, under these circumstances, was the result of the action of a humoral factor rather than of local oxygen deprivation in the bone marrow.

Oliva *et al.* (78), Seip (92), and Piliero and co-workers (80) relied on changes in the peripheral blood as an assay of erythropoietic activity in human plasma. Other experiments have used the Fe^{59} incorporation technic (50, 82). Matoth and co-workers (70) have employed short-term tissue cultures to demonstrate increased proliferation of human erythropoietic tissue in response to serum from anemic patients.

It has been suggested that the humoral stimulation of erythropoiesis may be only an emergency booster mechanism in times of stress (17). However, this theory would seem to be untenable in view of demonstrations of erythropoietin in normal human plasma (8, 50) and of data from investigations in which it was found that plasma from animals with transfusion-induced polycythemia has a decreased plasma erythropoietin content. We are inclined to postulate (51) that the production of red cells in man, like that in other mammals, is regulated continuously by the concentration of erythropoietin in the plasma (58).

Hodgson and Toha (54) first demonstrated the presence of erythropoietin in the urine of animals, and Piliero and co-workers (80) in that of anemic patients. This finding has been confirmed (52, 101), and promises to open a large area for clinical investigation. If normal human urine does not contain any erythropoietin, the possibility that the factor is a renal threshold substance would warrant further study. High urinary erythropoietin titers in patients with severe anemia facilitate study of changes in erythropoietin concentration, thereby elim-

inating the need for frequent phlebotomies (51). On several occasions, we have observed a decrease in the plasma and urinary erythropoietin titer of an anemic patient following transfusion (Fig. 3). This observation has also been reported by Medici *et al.* (71).

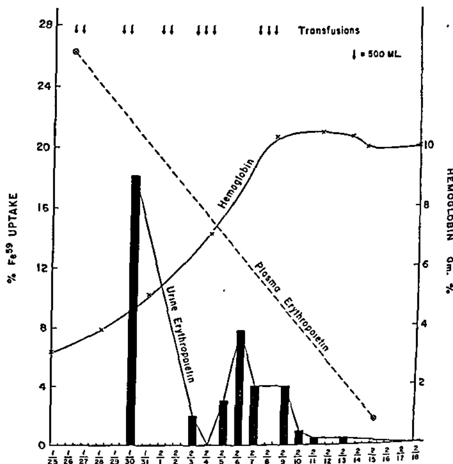


FIG. 3.—Fall in plasma and urinary erythropoietin titers after blood transfusions in a patient with aplastic anemia (preleukemia) (51).

It appears that many clinical anemias are accompanied by an elevation of erythropoietin in the plasma. This may be considered to be a response on the part of the site of production of erythropoietin *to* hypoxia. An adequate response leads to correction of the anemia if the bone marrow responds optimally. If the bone marrow responds suboptimally, the original response of the site(s) is of little or no consequence.

Many of the anemic patients we have studied, seem to have a refractory end-organ since the plasma erythropoietin titer is elevated but their bone marrow fails to respond sufficiently to restore the number of red blood cells to normal values. The plasma of all patients with aplastic anemia so far studied is characterized by a high erythropoietin titer, and the early hope (22) that this particular humoral regulator might play a therapeutic role in the control of this disease does not, at this time, appear promising.

However, the likelihood that some anemias are related etiologically to inadequate elaboration of erythropoietin or to its excessive destruction or excretion also deserves consideration because it is here that therapeutic implications are encouraging. Since at this time erythropoiesis-stimulating properties of normal plasma are demonstrable only with great difficulty, progress probably will be slow until more sensitive assay procedures are devised or until purified erythropoietin is available for clinical trials in anemic patients whose plasma does not assay positively.

Based on the belief that the erythropoiesis-stimulating action of cobalt results from the production of a high titer of erythropoietin, we have postulated (50, 51) that those anemias of man which accompany infection (88), starvation (3), chronic renal disease (9, 35), and neoplasia (93) may in some instances be attributable to reduced levels of circulating erythropoietin. If this reasoning is correct, one must then explain why the organ producing erythropoietin responds either directly or indirectly to cobalt and fails to respond to the state of anemia. One explanation might be that some of these "anemic" individuals, who still retain the capacity to respond to cobalt, actually may not be anemic in the sense that their oxygen demand is satisfied by their existing circulating red cell mass because the oxygen requirement is decreased coincidentally with the course of the disease. If this simple explanation of the nonfunction of the organ of erythropoietin production in patients with certain anemias is wrong, we have an interesting problem to solve, i.e., the paradoxic response of these patients to cobalt. One should probably continue to question the use of cobalt in some of the cases of "refractory anemia" until, in each instance, the mechanism of inhibition of erythropoietin production can be distinguished from nonutilization of the hormone.

There are experimentally induced disease states which can be used to support this thesis; in fact, these conditions are the basis of the assay methods we use, e.g., hypophysectomy or acute or subacute starvation. A response to cobalt or exogenous erythropoietin would be expected with these conditions, because the system is being forced into action.

Anemia, if it is defined on an arbitrary scale without regard to the relation of oxygen supply to demand, would not be expected to induce an increased production of erythropoietin in animals subjected to these various stresses.

It is of interest that we have failed to find a high titer of erythropoietin in the plasma of 7 anemic patients with chronic renal disease. Lange *et al.* (34), have supplemented this observation by demonstrating the erythropoiesis-stimulating properties of plasma from only 1 of 16 anemic patients with renal disease. They excluded impairment of erythropoiesis by a possible inhibitor by demonstrating that there was no reduction of response beyond that anticipated to result from dilution when the test plasma was mixed with active plasma before assay. Data from patients with chronic renal disease must be interpreted cautiously. Since, by the technics employed in these studies, erythropoietin cannot be demonstrated in normal plasma without previous concentration, all that can be said with certainty at this time is that a high titer is not present in plasma obtained from uremic anemic patients. It is conceivable, though unlikely, that normal titers of erythropoietin or even slight elevations, which are still below the lower limits of detection by the assay method employed, might be present in many of these plasma specimens. If the hormone titer is, as one suspects, lower than normal, then the anemia of renal disease is one of inadequate erythrocyte production, perhaps accentuated by hemolysis. It also seems possible that the anemia of chronic renal disease may be a combination of an over-all reduction in the metabolic oxygen requirement (and thus a reduction in erythropoietin production) or a reduced erythropoietin production caused by a pathologic change in site of production and by hemolysis. Results so far are suggestive, but obviously much clinical work remains to be done before the degree to which erythropoietin deficiency contributes to the anemia often associated with uremia is understood.

One unique refractory anemia has attracted the attention of several groups of investigators. Piliero *et al.* (80) found no erythropoiesis-stimulating properties in the extract of plasma prepared from the blood of a boy who had had hypoplastic anemia since birth. The authors considered it ". . . possible that there is an impaired capacity of such subject to elaborate the EP principle." Castle (17) agreed that "administration to these subjects of purified 'erythropoietin,' preferably from human sources, would be justifiable therapeutically" if the speculation proved to be correct. We, too, had considered the possibility that the congenital hypoplastic anemia of children (erythrogenesis imperfecta) might be a disease of erythropoietin deficiency because,

unlike aplastic anemia of adults, the hypoplasia in children, as would be expected, is limited to the erythrocyte precursors. In collaboration with Drs. Mila Pierce, Stanley Shrier, and Paul Carsten (53), we therefore undertook an investigation of this condition. The results have not yet been reported in detail. Chronic administration of plasma obtained from anemic donors produced a reticulocyte response in 2 patients. This change was not obtained subsequently in 1 of the children when comparable amounts of plasma were given after the hemoglobin level of the same donors had been raised above normal levels by means of transfusions. However, the plasma obtained from both children, as well as that from a third child with this syndrome, was found to be extremely rich in erythropoietin, as determined by measuring the Fe^{59} incorporation into the red blood cells of rats. Clearly, then, the disease in the 3 patients cannot be attributed to a deficiency of erythropoietin in the plasma. Nevertheless, some factor able to stimulate a mild reticulocytosis in these children appears to be present in plasma from donors rendered acutely anemic by phlebotomy.

A later report by Medici and associates (71) states that further studies of plasma extracts from the patient with chronic hypoplastic anemia whose plasma extract had given negative results when first assayed for erythropoietin (80), now gave positive results.

High titers of erythropoietin have been found in the extracts of plasma from some patients with polycythemia vera (2, 20, 66). This is unusual because the action of erythropoietin seems to be limited to the erythroid series, and polycythemia vera is usually a panmyelopathy. Clearly, the entire clinical picture cannot be attributed to a high titer of erythropoietin in the plasma.

The increased red cell production seen in secondary polycythemia would be expected to be associated with, and be the consequence of, increased plasma erythropoietin concentrations. Recently, we have assayed the plasma from 2 patients with polycythemia associated with hypernephroma.* In both instances, elevated concentrations of erythropoietin were demonstrated. We found this result to be of particular interest because we had demonstrated the role of the kidney in erythropoietin production. An increasing number of patients with hypernephroma and polycythemia has been reported in recent years (18, 23, 31). Attempts to extract erythropoietin from this tumor might be profitable. However, our concept of the regulation of erythropoiesis by erythropoietin leads us to expect that increased erythropoietin production would be the rule in all cases of secondary polycythemia, re-

* Plasma specimens were kindly supplied by Dr. Fred Zimmer and Dr. M. Wintrobe.

gardless of the cause. The high erythropoietin titers in plasma of cord blood (1, 24) is consistent with this.

Little is known about utilization of erythropoietin, but many of our observations in clinical studies suggest that erythropoietin may be consumed or degraded in the process of stimulating the marrow. It is therefore appropriate that we should summarize our concept of the dynamic equilibrium of erythropoiesis as it pertains to clinical problems with the following comments and speculations pertaining to production and utilization of erythropoietin.

If the severity of a stimulus such as hypoxic or anemic anoxia were to be gradually increased, erythropoiesis could be expected to increase as erythropoietin production increased. However, it is quite possible that the plasma titer of erythropoietin would not be measurably above the normal (by current methods of assay), and therefore no measurable amount would be excreted. In other words, utilization might parallel production. This concept would explain our observation that assay of plasma from patients with a moderate anemia but with an active marrow, such as in patients with hemolytic or pernicious anemia, may reveal little or no erythropoietic activity. If, however, the stimulus were severe and abrupt, one would expect to find erythropoietin in the plasma and, perhaps, in the urine as well, because erythropoiesis could not increase rapidly enough to utilize available erythropoietin. Similarly, if the stimulus were increased gradually, only as soon as erythropoiesis reached its maximum (calculated to be six times normal) would excess erythropoietin be found in the plasma and perhaps in the urine, and then only if the stimulus for, and actual production of, erythropoietin exceeded utilization.

In patients with aplastic or hypoplastic anemia, erythrogenesis imperfecta, and some leukemias, as described by Gurney *et al.* (50), erythropoiesis is minimal and hence an anemia exists. In such cases, as expected, the erythropoietin titer is high in both plasma and urine. Under these conditions minimal or no utilization might be expected, yet a normal or high erythropoietin production is maintained. In these patients, production of erythropoietin can be stopped by transfusion, i.e., the erythropoietin titer in blood and urine falls to normal as the red cell count and hemoglobin rise toward the normal range. In other words, the normal mechanism (anemic anoxia) exists and the normal response occurs (increased erythropoietin production); by reducing the stimulus (transfusion), erythropoietin production falls.

In other patients, no response to anemic anoxia may occur, as measured by plasma or urine erythropoietin titer. In most cases, this can be explained on the basis of nutritional factors, infection, renal dis-

eases, etc. In others, an anemia may exist in response to decreased metabolism (hypothyroidism or hypophysectomy), in which no anoxic stimulus exists and production and utilization of erythropoietin are in equilibrium.

Further clinical progress in elucidating the significance of erythropoietin is to be anticipated. Many questions await answers. To a large degree, however, clinical progress must await advances in biochemistry and physiology. More sensitive assay methods are desirable. Purification of erythropoietin and its production in amounts large enough to warrant large-scale trials are destined to open a new area of clinical investigation. Regardless of any limitations of the clinical usefulness of erythropoietin which future investigations may disclose, studies in recent years have substantially furthered our understanding of some of the basic aspects of red cell formation.

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Bronchiolo-Alveolar Carcinoma

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NEW INSIGHTS into the natural history of pulmonary diseases have been provided by "survey films," although these have not met with unanimous approval because of the radiation involved. Conditions formerly encountered only when they had become symptomatic are now known to represent late stages in a long evolution. Some tumors seemingly central when seen late actually have been traced to a more peripheral origin (109). Others that might be considered multicentric have been traced roentgenographically to a single focus. To this group belong the controversial tumors for which the term "bronchiolo-alveolar" has been chosen in the following discussion.

During a recent discussion of the classification of lung tumors at an international meeting assembled for the purpose, there was surprisingly little objection to applying this term to a group of peripheral pulmonary neoplasms which pursue a rather characteristic course when permitted to progress untreated. This Solomon's judgment regarding terminology does not, however, imply unanimity of opinion with respect to details. I have previously listed some terms considered more or less synonymous (82), Laipply (77) has added others, and even this does not encompass the total. Suffice it to say, that for present purposes "bronchiolar carcinoma," "alveolar cell tumors," and "pulmonary adenomatosis," will be considered as synonymous with "bronchiolo-alveolar carcinoma," with the implication that attempts to establish distinctions (7, 8) have not proved convincing.

DEFINITION

The bronchiolo-alveolar tumors can be most simply defined as generally well-differentiated adenocarcinomas primary in the periphery of the lung beyond a grossly recognizable bronchus, with a tendency to

spread chiefly within the confines of the lung by aerogenous and lymphatic routes, the walls of the distal air spaces often acting as supporting stroma for the neoplastic cells.

With any other definition (except the untenable one that assumes knowledge of the "cell of origin"), the question will at once arise of distinguishing bronchiolo-alveolar carcinoma from "ordinary" adenocarcinoma of the lung. In my opinion, such a distinction cannot be made at present. The important point is that good cytologic differentiation and very peripheral origin are correlated with the tendency to spread *within the lung*, by which means such tumors can even produce death without metastasis. On the contrary, poorly differentiated adenocarcinomas arising in small but identifiable bronchi tend to be among the most malignant pulmonary tumors, with a rapid local growth rate and capacity for quick distant metastasis via the blood stream, but without neglecting the lymphatic channels. It must therefore be acknowledged that no definition has succeeded in separating certain intermediate forms, especially since envelopment of bronchi will inevitably occur in the course of growth of even the most peripheral lesions. Thus some variation will persist in precisely what pulmonary tumors are considered "bronchiolo-alveolar" until histochemical or other objective distinguishing properties can be established.

To insist that tumors to be called bronchiolo-alveolar grow on the "unaltered walls of alveoli," or "without destruction of pulmonary architecture," is to add confusion, since some of the illustrations presented usually show both of these changes in varying degree. It must also be recognized that metastatic tumors can spread in a manner indistinguishable from that of bronchiolo-alveolar carcinoma. A primary source outside the lung must therefore always be excluded before the latter diagnosis is made.

HISTORICAL NOTES

Malassez (91) is generally credited with the first description of the metastasizing multinodular stage or form of the disease in 1876, and Musser (97) with that of the diffuse or "pneumonic" form in 1903. Another early description of a lesion of the latter type was that of Ravenna (107). Musser clearly understood that it was the close spacing of innumerable minute nodules that produced the gross appearance of diffuseness. Helly (58) first described an example of the multinodular form which had remained confined to the lung. The first localized tumor of this group to be reported was by Löhlein (84), who found it incidentally at autopsy. Bonné (14) forcefully pointed to the simi-

larities of bronchiolo-alveolar tumors to certain diseases of animals and thus started much speculation and some investigation.

The first diagnosis made during the life of a patient was apparently by Škorpil (117), who reported the 5 year survival of a patient on whom a lobectomy had been performed in 1936. It is of special interest that metastases were found in large nodes in the hilum of the lobe removed at operation. This is also the first reported surgical success in dealing with this lesion.

INCIDENCE OF BRONCHIOLO-ALVEOLAR TUMORS

Estimates of the incidence of bronchiolo-alveolar tumors have varied from 0.5 to 5 per cent of all carcinomas of the lung (7, 28, 32, 35). These figures are in part affected by nuances of definition, and in part by whether primarily surgical or autopsy material is reviewed. Since in most large series adenocarcinomas in general constitute only about 15 per cent of all lung tumors (82), the 5 per cent figure for bronchiolo-alveolar tumors seems too high. In the combined reports from 4 sizeable series in which numerical information on all lung tumors as well as on bronchiolo-alveolar tumors specifically is given (50, 101, 125, 130), the incidence of bronchiolo-alveolar carcinoma is 2 per cent. An impression that the prevalence of these tumors has increased (12) requires confirmation.

PATHOLOGY

Gross Features

Bronchiolo-alveolar tumors present grossly in three main forms: *(1)* as an isolated nodule; *(2)* as multiple nodules; and *(3)* as a diffuse, or "pneumonic" lesion. According to Eck (32) on the basis of 232 cases, 57 per cent of the lesions are nodular, 26 per cent are "lobar" (diffuse), and 17 per cent are mixed. In his series, 24 per cent appeared to be confined to the right lung, 22 per cent to the left, and 54 per cent were bilateral. These data are not far different from those of Storey and coworkers (123), who stated that over 67 per cent appeared to be unilateral by radiographic criteria.

Isolated nodular form.—It has now been well established that a solitary small tumor less than 4 cm. in diameter can be microscopically identical with the myriads of the disseminated disease. It is astonishing that some pathologists of wide experience do not recognize this type. Existence of the isolated form at once implies origin in a single focus, and also the possibility of surgical cure.

In the isolated form, the lesion varies in appearance from case to case (3, 7, 12, 25, 30, 55, 84, 99, 109, 110, 123, 130). Approximately two-thirds occur in the upper lobes (130). Some are almost spherical, sharply circumscribed although not encapsulated, gray-pink, pale yellow, or almost white in color and of resilient firmness. Glairy mucinous material may be evident on the cut surface. Such lesions usually do not show cavitation unless they reach a large size.

Others are more poorly defined, and may actually be difficult to recognize as tumor with the naked eye, although they may have appeared as a mass radiographically. This is because they may be merged with scar tissue, having either begun at the margin of a scar, or having themselves become scarred as a result of infarction or some other mechanism of necrosis. Neubuerger and Geever (98) remarked upon the scarring in some of their cases. In such cases, the lesion is puckered, poorly defined from surrounding partially scarred tissue, deeply pigmented with anthracotic material, and suggestive of tumor only because of a pearly translucency and greater softness in some part (Plate 1, *A*).

Massive necrosis is rare in bronchiolo-alveolar carcinoma, but sometimes there is a subtle form of destruction resulting in the production of mucus-filled cavities the lining of which may appear quite intact for the most part. Cavitation in general is reported to occur in approximately 20 per cent of these tumors (50), more commonly in the larger localized primary foci.

Disseminated nodular form.—The disseminated nodules tend to be like the first of the two types of isolated lesion described. They are then similar to metastatic carcinoma, or, in some instances, to multiple pneumonic foci or disseminated granulomas (Plate 1, *B*).

In some patients after the roentgenographic demonstration of an apparently isolated lesion, disseminated nodules have subsequently been observed (Plate 2). In certain of these tumors, cavitation and pigmentation are striking at the initial site (Plate 1, *C*) which will usually have given radiographic evidence of increase in size. The scattered nodules, however, are little if at all pigmented. When the latter have become confluent, however, cavitation can occur (Plate 1, *D*); this may also affect some of the isolated nodules (9).

Diffuse form.—Grossly, there is a form which resembles diffuse pneumonia (Plate 3, *A*) in the stage of gray hepatization. The tissue, however, is more firm and more translucent, and tends to be pink. Again, a glistening mucoid fluid may exude from the cut surface. The tissue so altered may be vaguely defined from the surrounding parenchyma, in part because the latter may have become partly or even

massively consolidated and rendered airless because of aspiration of mucoid material (Plate 3, *B*). Cavitation may occur in this form, too (28, 35, 138).

On close inspection, Musser's (97) view that the lesion in fact consists of multiple minute nodules is confirmed (Plate 3 *C*).

Histologic Features

The appearance of the neoplastic epithelium varies from case to case, and sometimes from field to field in the same tumor. At one extreme it consists of a single layer of regular, tall, pale-staining, mucus-producing cells with basally placed nuclei among which mitoses are extremely difficult to find (Plate 4, *A*). The stroma can be thin, and preponderantly that of existing distal air spaces with little alteration. The appearance can be so benign that the term "adenomatosis" has been used. This form resembles an infectious disease of sheep. However, it still remains to be determined whether such tumors in man are actually less prone to metastasize than others in the group. Certainly metastases do occur in some instances, as in the ovine disease (14, 22, 31). It is also noteworthy that foci of malignant-appearing cells can occur in otherwise well-differentiated lesions in man (23, 28, 66).

Other tumors consist of less regular cells, still with abundant cytoplasm which is characteristically acidophilic (Plate 5, *A*). The cells may project irregularly into the lumen in "saw-tooth" fashion, and papillary formations result from infolding of the stroma or from piling up of epithelium in about 75 per cent of these neoplasms (53). The latter process may lead to the complete filling of some acini. In the papillary forms, the cells are more often cuboidal than cylindric (Plate 4, *B*). Occasionally, the cells are bizarre and may be gigantic. In the less regular epithelial cells, the nuclei also vary in size and in intensity of staining, being at times quite hyperchromatic. Even in these tumors mitoses are uncommon.

Mucus is demonstrable in some portions of most of these tumors (53). It is usually abundant in the more differentiated forms, and scanty or absent in the cuboidal, papillary, and irregular epithelial types (126). According to Fair *et al.* (34), it is present in approximately 80 per cent of all adenocarcinomas and the figure for the bronchiolo-alveolar type is much the same. Fat can also occur within the tumor cells (123).

Statements regarding the presence of cilia have varied widely. I have seen cilia only in a single example out of some 20 bronchiolo-alveolar tumors. They are commonly present in the acinar type of

atypical proliferation with which bronchiolo-alveolar tumors can be associated (12). Since Laipply, in particular, has referred to the more striking forms of this process as "bronchiolar adenoma," it is not surprising that his reports have suggested that cilia occur frequently (77, 79). Others have found them in none of their cases (98, 115).

Squamous metaplasia in bronchiolo-alveolar carcinoma, too, is rare (Plate 5, *B*), but I have seen it in 3 of 20 tumors which otherwise fit well into the group; it has also been reported by others (10, 45, 102, 119). This type of change should not occasion too much surprise, as it exists in association with the acinar type of atypical proliferation and in many adenocarcinomas, including those of the lung.

The preparation of multiple sections will reveal calcification (Plate 6, *A*), usually in the form of rounded, lamellated, psammoma bodies, in almost 50 per cent of all bronchiolo-alveolar tumors (119). It is especially likely to be present in the stroma of the papillary forms. As a rule, the calcification is too slight to be visible as such radiographically. Ziegler (141), however, has reported an example of a strikingly calcified tumor of this group.

In some part of the isolated nodular form, the stroma usually is densely hyaline connective tissue, in confirmation of the gross appearance. Only at the very periphery of such a lesion may the stroma be relatively thin and represent in part the walls of pre-existing air spaces, of a structure corresponding more or less to the appropriate level of the respiratory tree, but usually with some infiltrate of leukocytes, some fibrosis, or both. The "classic" appearance of an entirely intact parenchyma acting throughout as the sole support of the neoplastic cells is imaginary, and it is more closely approximated in the lesions of the multinodular and "pneumonic" forms. This is perhaps because these forms are probably the result of "seeding" from a single primary site. Even in these forms, fibrosis of the stroma may occasionally be so prominent as to deserve the designation, "desmoplastic reaction" (Plate 6, *B*). Even the cells of tumors *metastatic* to the lung, however, may be supported by the walls of alveoli (16, 32).

Relation to bronchioles and bronchi.—Inspection of a lung which is the seat of the multinodular or diffuse form of the disease usually reveals the lesions to be clearly centered upon bronchioles, and that the epithelium of the latter is often partly or completely replaced by the epithelium of the tumor (Plate 6, *B*). In fact, normal bronchioles of a certain size may be difficult to find in field after field, while those more proximal appear to be intact. Uniformity in the size of the involved bronchioles is sometimes striking, but there may be variations in other instances.

The contrast between normal and neoplastic epithelium is usually quite sharp at the point of junction (Plate 6, *C*). Hutchison (64) and Hutchison and Fraser (65), however, have noted the presence of "transitional forms" in the lining membranes of some distal air passages. These do not necessarily possess histogenetic significance.

Prominent papillary ingrowths of neoplastic epithelium into the lumens of the bronchioles can sometimes be observed (Plate 7, *A*) and this may be a prominent feature, especially when there is only a solitary nodule of tumor. Gepts (48) has described peculiar "diverticular" outgrowths from bronchioles in his case, lined largely by neoplastic epithelium, but in part also by normal ciliated bronchial cells of the surface; there was also an overflow upon the adjacent surface of the bronchiole of atypical epithelium from some of the "diverticula." The latter he considered to be congenital, but another interpretation is that they are the result of implantation of neoplastic epithelium upon the surfaces of bronchioles which then proceeds to grow extrinsically to form the outpouchings, rather than intrinsically to form papillae.

Lambert (80) has pointed out the existence of congenital "accessory communications" (canals) of bronchioles with adjacent alveoli. It is certainly possible that tumor cells can utilize these as a means of access to such alveoli (Plate 7, *B*), but their number is normally too small to account for the findings in Gepts case. In chronic pulmonary disease, however, where atypical proliferation of the acinar type is common, defects in the walls of bronchioles lined by proliferating epithelium become numerous (15). These are more numerous than the canals of Lambert, and may be considered to be analogous to the Rokitansky-Aschoff sinuses in the gallbladder. Thus, even in the benign regenerative hyperplasia, epithelium continuous with that of bronchioles can gain access by accessory routes to adjacent alveoli, and the process in neoplasia is analogous.

Relation to Atypical Proliferation and Fibrosis

Bronchiolo-alveolar carcinoma is often associated with, and sometimes difficult to distinguish from, atypical proliferation of the acinar type. For this reason a discussion of this subject is indicated. It is well known that cells lining distal air spaces often become taller than usual, and sometimes atypical, in the presence of interstitial or massive fibrosis of chronic pulmonary disease (4, 75, 133). Electron microscopy has now provided direct evidence of the existence of a continuous epithelial lining in the normal alveolus (72, 85, 137), which at lesser magnification is inconspicuous. Thus the conclusions drawn by Cap-

pell (17) and later by El Gazayerli (33) that such cells could change in response to various influences has been supported. They differed in that the latter stated that only certain special "septal" cells could give rise to phagocytes in the alveoli, while Cappell claimed that the lining cells generally could be the source of the phagocytic elements.

The source of the proliferated lining cells seen in pulmonary disease has been ascribed variously to proliferation *in situ* within alveoli, of either of the cell types just mentioned (13, 69), or to downgrowth in continuity with the lining cells of bronchioles. Some have claimed to be able to distinguish the source of the proliferating cells (12, 131), but any such attempt requires the supporting evidence of serial sections to be plausible. Others, e.g., Herbut (61, 62), have stated that the epithelium is derived by downgrowth from the lining cells of the bronchioles, a view supported by the experimental work of Moran (95) and Moran and Hellstrom (96).

It is not only the hyperplasia but also the atypical appearance of the regenerating cells in pulmonary disease that has prompted questions of whether they can give rise to neoplasia. This suggestion was made long ago in relation to influenza (4, 133), but in this disease the metaplasia is largely squamous. Highly atypical epithelium is also commonly observed at the margins of infarcts (118).

One particular type of acinar atypical proliferation is often confused with bronchiolo-alveolar carcinoma, and it is actually possible that the latter can develop on the basis of this lesion. Grossly, the lesion may appear simply as a zone of more or less vaguely defined "fibrosis," sometimes with a shining surface from which mucus can be scraped, and in other instances having the appearance of "honeycombing" of various degrees of coarseness. The latter, however, is nonspecific and may be the result of unrelated processes such as Letterer-Siwe disease (60, 100). The superior portions of the upper and lower lobes are most frequently involved in the "honeycombing." In such instances a reticular pattern may be visible radiographically; when the process is disseminated and involves all lobes, mottled, floccular, and reticular densities may be visible in the corresponding distribution on the roentgenograms. The lesion under discussion is complex and consists of: *(1)* loss of alveoli, together with disappearance of the septa among them and overdistention of distal air spaces including bronchioles, as in emphysema; *(2)* varying degrees of interstitial fibrosis of the remaining tissue, often accompanied by muscular hyperplasia; and *(3)* downgrowth of mucus-producing, ciliated, or flattened epithelium from the bronchioles into the varyingly enlarged air spaces that form the honeycomb (Plate 8, *A*). The epithelium gains access to these not only along

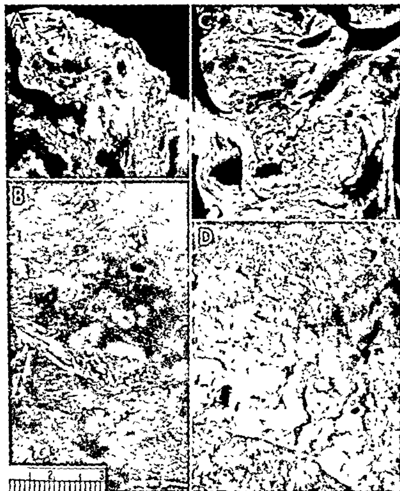


PLATE 1.—Bronchiolo-alveolar tumor A, isolated nodule associated with scarring in right upper lobe, tumor identifiable as white mottling near margins of deeply pigmented scar, for histologic appearance *see* Plate 8, *B* **B**, "multinodular" form; slightly elevated nodules appear gray-tan in the fresh, with small focal deposits of anthracotic pigment at margins; for histologic appearance, *see* Plates 4, *B* and 7, *B*. **C**, multinodular" form, rear view of left lower lobe in frontal section; lesion was first demonstrated in left lower lobe; subsequently it spread (Plate 2); site of first lesion became cavitated, scarred, and puckered, with more anthracotic pigment than elsewhere, adjacent pleura adherent and invaded locally, with formation of thick-walled loculus, metastases in bronchial lymph nodes, but no evidence of extrathoracic metastases **D**, same patient as in C, right upper lobe *(above)* and portion of right middle lobe *(below transverse fissure)*, some nodules resemble those in lung of patient in *B*, but they have become confluent and a small cavity has formed, no obvious necrosis, however, in wall of this cavity.

pell (17) and later by El Gazayerli (33) that such cells could change in response to various influences has been supported. They differed in that the latter stated that only certain special "septal" cells could give rise to phagocytes in the alveoli, while Cappell claimed that the lining cells generally could be the source of the phagocytic elements.

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PLATE 5.—"Pneumonic" form of bronchiolo-alveolar tumor. A, vaguely defined ground-glass opacity in hilar region of right lower lobe, for bronchogram, *see* Plate 12, *A*. *Lobectomy was performed* (*B* and *C*), but patient died within the year as result of tumor dissemination throughout remaining lung tissue. Autopsy not performed. B, right lower lobe specimen, from a distance, tissue near hilum *appeared pink and firm, and exuded considerable mucus; closer inspection* (*C*) belied diffuse nature of lesion, more laterally lung was firm and airless, largely because of aspirated mucus as demonstrated microscopically, on diaphragmatic *aspect, deeply retracted scarred mass of tumor tissue, interpreted as representing* site of original lesion. C, close-up of portion of lung shown in *B*, despite "diffuse" appearance of lesion when viewed at distance, multiple minute nodules may be seen.

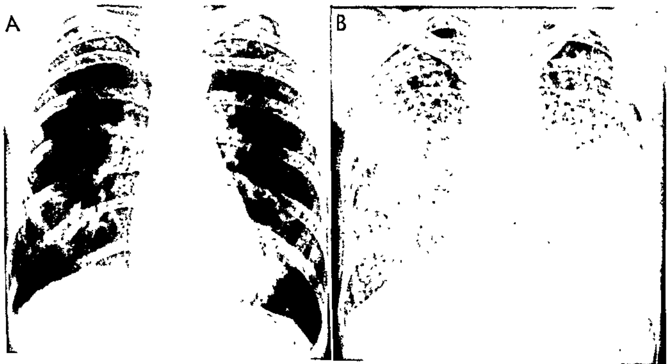


Plate 2.—Bronchiolo-alveolar tumor. *A*, same patient as in Plate 1, *C* and *D*, February, 1950; single shadow in left lower lobe; patient was in tuberculosis sanatorium, and lesion was at first considered to be an unresolved pneumonia; by April, 1950, lesion had grown somewhat larger, and several similar, but smaller, foci had appeared on right side. *B*, same patient, December, 1953; note miliary and confluent nodular lesions; patient died in January, 1954. This plate gives evidence of dissemination from single focus; appearance similar to that of patient in Plate 1, *B*, but no earlier films were available in latter case.



PLATE 3.—"Pneumonic" form of bronchiolo alveolar tumor. A, vaguely defined ground-glass opacity in hilar region of right lower lobe; for bronchogram, *see* Plate 12, *A*. Lobectomy was performed (*B* and *C*), but patient died within the year as result of tumor dissemination throughout remaining lung tissue. Autopsy not performed. B, right lower lobe specimen, from a distance, tissue near hilum appeared pink and firm, and exuded considerable mucus; closer inspection (*C*) belied diffuse nature of lesion; more laterally lung was firm and airless, largely because of aspirated mucus, as demonstrated microscopically; on diaphragmatic aspect, deeply retracted scarred mass of tumor tissue, interpreted as representing site of original lesion. C, close-up of portion of lung shown in *B*; despite "diffuse" appearance of lesion when viewed at distance, multiple minute nodules may be seen



Plate 4.—*A*, well-differentiated bronchiolo-alveolar carcinoma; tall, mucus producing columnar cells with basally placed nuclei; mitoses extremely rare septa among acini may represent alveoli, but if so they have become thickened and infiltrated with mononuclear cells: grossly, tumor had appearance of "pneumonic" form Death occurred within a year after pneumonectomy due to tumor extension into remaining lung tissue Same patient as in Plate 6, *B* and *C*. B, bronchiolo-alveolar tumor with papillary formations, cells are cuboidal, do not produce mucus, and are less regular than in specimen shown in *A*, mitoses are extremely rare Same patient as in Plates 1, *B* and 7, *B*



PLATE 5.—Bronchiolo alveolar tumor. A, tall columnar cells, in part stratified or pseudostratified, supported by thin stroma, resembles intact interalveolar septa, but this interpretation may not be correct, since similar stroma can be seen in metastases (*see* Plate 10, *B*). B, another field in same tumor as in *A*, showing squamous change; squamous epithelium is somewhat irregular, but does not suggest malignancy; change is reminiscent of that seen in "acinar atypical proliferation" (cf. with Plate 8, *A*).



PLATE 4.—A, well-differentiated bronchiolo-alveolar carcinoma; tall, mucus-producing columnar cells with basally placed nuclei, mitoses extremely rare, septa among acini may represent alveoli, but if so they have become thickened and infiltrated with mononuclear cells, grossly, tumor had appearance of "pneumonic" form. Death occurred within a year after pneumonectomy due to tumor extension into remaining lung tissue Same patient as in Plate 6, *B* and *C* B, bronchiolo-alveolar tumor with papillary formations; cells are cuboidal, do not produce mucus, and are less regular than in specimen shown in *A*; mitoses are extremely rare. Same patient as in Plates 1, *B* and 7, *B*



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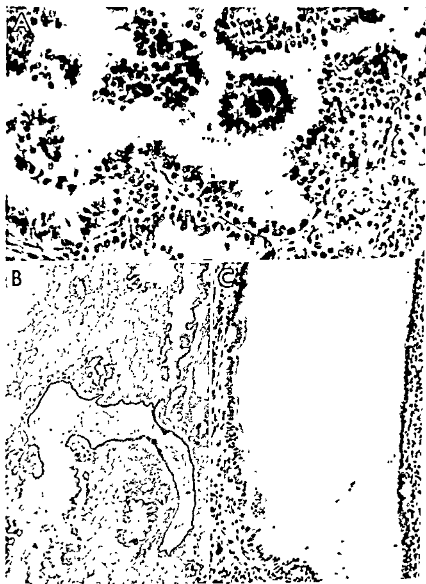


PLATE 6.—Bronchiolo-alveolar tumor A, with calcification of stroma, irregular, low, columnar, mucus-producing epithelium with some papillary formations, same tumor as in Plate 7, A. B, well-differentiated form (same tumor as in Plates 4, A and 6, C), bronchiole lined proximally by typical epithelium *(dark)*, replaced along longitudinal course of bronchiole by taller, pale-staining tumor cells in a manner suggesting origin in this bronchiole or implantation of aspirated epithelium, but not envelopment by a focus of tumor arising in associated alveoli. C, same tumor; sharp contrast without transition between atypical epithelium of tumor and ciliated normal epithelium of bronchiole



PLATE 7.—Bronchiolo-alveolar tumor A, terminal bronchus (note cartilage at right and below), with well-differentiated papillary tumor which elsewhere grows in acinar form supported in part by stroma of alveoli (cf. with Plate 6, *A*). B, bronchiole, lining cells of which have been replaced by atypical epithelium projecting into lumen in papillary fashion, and penetrating through wall, as if through canal of Lambert, to line adjacent labyrinth (same tumor as in Plates 1, *B* and 4, *B*).



PLATE 8.—A, acinar atypical proliferation, extreme example of a regenerative process considered benign, some distal air spaces are lined by ciliated columnar cells, others by tall, mucus-producing or, occasionally by squamous cells, gross appearance is that of interstitial scarring and "honeycombing" widely disseminated throughout all lobes this process is much more often localized in upper portions of upper and lower lobes B, bronchiolo-alveolar tumor associated with scar, tumor lies preponderantly at margin of large, pigmented scar, but a few atypical acini are within the latter *(left and below)*



PLATE 9.—*A*, bronchiolo-alveolar type of tumor in a single nodule in lung of a 7 year old spaniel dog; focal calcification *(near right border)*, appearance resembles somewhat that of human tumor in Plate 6, *A* (Section supplied by Dr. C F. Helmboldt, University of Connecticut) B, "adenomatosis" of sheep, Peruvian form; lesion is centered on branches of bronchiole, resembling human lesion in Plate 6, *B*. (Sections supplied by Dr A Cuba-Caparó, Yale University School of Medicine)



PLATE 8.—A, acinar atypical proliferation; extreme example of a regenerative process considered benign, some distal air spaces are lined by ciliated columnar cells, others by tall, mucus producing or, occasionally by squamous cells; gross appearance is that of interstitial scarring and "honeycombing" widely disseminated throughout all lobes, this process is much more often localized in upper portions of upper and lower lobes. B, bronchiolo alveolar tumor associated with scar, tumor lies preponderantly at margin of large, pigmented scar, but a few atypical acini are within the latter *(left and below)*



PLATE 11.—A, metastasis to lung from carcinoma of gallbladder; in this subpleural nodule epithelium grows like a bronchiolo-alveolar tumor, being supported in part by stroma of distal air spaces; appearance of mucus producing epithelium of this well-differentiated tumor is identical with that of primary lesion, aerogenous dissemination of tumor reaching lung via blood stream or lymphatics is responsible for this appearance B, bronchiolo-alveolar carcinoma (same tumor as in Plate 5); compression of large blood vessel and its branches.



PLATE 10.—"Adenomatosis" of sheep Peruvian form (same animal as in Plate 9, *B*) A, papillary ingrowth into bronchiole; opposite wall *(at right)* lined by ciliated epithelium; relation similar to that in human lesion, Plate 7, *A*. B, metastasis in lymph node, epithelium here is less regular than in lung itself; delicate stroma supports papillary tumor, but is obviously not alveolar.

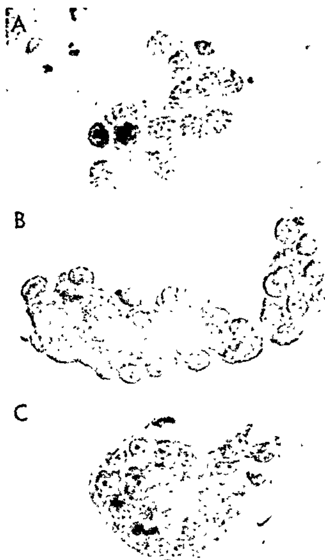


PLATE 13.—A, clump of cells in sputum of patient with bronchiolo-alveolar tumor; larger than normal cells, size of nuclei varies slightly more than in normal cells, and nucleoli are more prominent, grouping is characteristic, but not pathognomonic (cf. with *B* and *C*). B, large cylindrical clump of cells from bronchogenic adenocarcinoma, somewhat more variation than in *A*. C, clump of nonciliated tumor cells in sputum of patient with multiple pulmonary metastases from carcinoma of sigmoid, cells are obviously mucus producing; occurrence of clumps not unusual in metastatic tumors



PLATE 12.—Bronchiolo-alveolar carcinoma (same tumor as in Plate 3). A, bronchogram, showing elongated, narrowed, rigid-looking bronchioles, with linear densities in periphery of isolated Lipiodol resembling exclamation points; no "alveolar filling" in lower and middle lobes. Signs described by Zheutlin and associates (140). B, mechanism of bronchographic change, bronchial wall rendered rigid by desmoplastic reaction; lumen largely not narrowed, but distally some of its branches are obliterated by surrounding dense, fibrous connective tissue.

the surfaces of the descending orders of bronchioles, but also via the accessory bronchiolo-alveolar communications of Lambert (80), and the additional newly formed channels of this type that are analogous to Rokitansky-Aschoff sinuses (15). All transitions may be found to be ordinary emphysema.

It is important to understand that there is a notable revision of the architecture of the distal air spaces, and that it may no longer be possible to identify any particular space, such as an alveolus or alveolar duct. Many of these spaces contain components of several levels in the normal sequence of branching but more or less altered, and some are in direct connection with rather proximal orders of bronchioles. The epithelium is often hyperplastic, sometimes atypical, and occasionally squamous. It is apparently lesions of this type that, when diffuse, Laipply and co-workers have in more recent publications called "bronchiolar adenoma" (77, 79). This designation, however, does not seem justified in view of the fact that focal acinar epithelial proliferation is common in the lungs of older people. In a recent study it was found in more than 5 per cent of routine sections at autopsy of persons between the ages of 70 and 90, and in over 20 per cent of the lungs in those 90 years or older (15). These are minimal figures based simply on the study of routine sections from autopsy files. Also, it is frequent in persons with focal organizing pulmonary disease at any age, and it has been produced experimentally (94–96). Moreover, such changes occur commonly in association with the dense interstitial fibrosis of "diffuse sclerosis" as it involves the lung, again to produce a "honeycomb" pattern (49, 68, 90, 108, 139). In view of these facts, acinar atypical proliferation is best regarded simply as a regenerative phenomenon which is usually self-limited, although often exuberant and atypical.

The relation of atypical proliferation of this type to bronchiolo-alveolar carcinoma has long been suspected. Bell (13), in 1943, illustrated a case of acinar atypical proliferation, and another that would fit the present description of bronchiolo-alveolar carcinoma, and remarked on their similarity. In the same year, Geever, Neubuerger, and Davis (46), who also considered the cells to be derived from alveolar lining, diagrammed possible transformations through various stages finally to "anaplastic septal cells." In the report by Laipply (77) which *introduced the term "bronchiolar adenoma," it is admitted that "in* fact sections of some bronchiolar adenomas showing dilated alveoli lined with epithelium, marked interstitial fibrosis, and lymphocytic infiltration, are suggestive of bronchiolectasis and chronic pneumonitis." Most observers would in fact conclude that this is exactly what

the surfaces of the descending orders of bronchioles, but also via the accessory bronchiolo-alveolar communications of Lambert (80), and the additional newly formed channels of this type that are analogous to Rokitansky-Aschoff sinuses (15). All transitions may be found to be ordinary emphysema.

It is important to understand that there is a notable revision of the architecture of the distal air spaces, and that it may no longer be possible to identify any particular space, such as an alveolus or alveolar duct. Many of these spaces contain components of several levels in the normal sequence of branching but more or less altered, and some are in direct connection with rather proximal orders of bronchioles. The epithelium is often hyperplastic, sometimes atypical, and occasionally squamous. It is apparently lesions of this type that, when diffuse, Laipply and co-workers have in more recent publications called "bronchiolar adenoma" (77, 79). This designation, however, does not seem justified in view of the fact that focal acinar epithelial proliferation is common in the lungs of older people. In a recent study it was found in more than 5 per cent of routine sections at autopsy of persons between the ages of 70 and 90, and in over 20 per cent of the lungs in those 90 years or older (15). These are minimal figures based simply on the study of routine sections from autopsy files. Also, it is frequent in persons with focal organizing pulmonary disease at any age, and it has been produced experimentally (94–96). Moreover, such changes occur commonly in association with the dense interstitial fibrosis of "diffuse sclerosis" as it involves the lung, again to produce a "honeycomb" pattern (49, 68, 90, 108, 139). In view of these facts, acinar atypical proliferation is best regarded simply as a regenerative phenomenon which is usually self-limited, although often exuberant and atypical.

The relation of atypical proliferation of this type to bronchiolo-alveolar carcinoma has long been suspected. Bell (13), in 1943, illustrated a case of acinar atypical proliferation, and another that would fit the present description of bronchiolo-alveolar carcinoma, and remarked on their similarity. In the same year, Geever, Neubuerger, and Davis (46), who also considered the cells to be derived from alveolar lining, diagrammed possible transformations through various stages finally to "anaplastic septal cells." In the report by Laipply (77) which introduced the term "bronchiolar adenoma," it is admitted that "in fact sections of some bronchiolar adenomas showing dilated alveoli lined with epithelium, marked interstitial fibrosis, and lymphocytic infiltration, are suggestive of bronchiolectasis and chronic pneumonitis." Most observers would in fact conclude that this is exactly what

the condition represents. Some of the cases of true bronchiolo-alveolar carcinoma reported by Laipply *et al.* (79) were shown to be associated with this lesion. A similar instance with some spaces lined by cilia is illustrated by Swan (125) (case 3), and others are reported by Spencer and Raeburn (121). Various other workers have also recently given thoughtful consideration to the relation between chronic pulmonary disease and bronchiolo-alveolar tumors (10, 12, 18, 21, 23, 120). Of Baló's (7) 11 "alveolar-cell tumors," 5 were associated with scarring. In Beaver and Shapiro's (12) review of 120 cases, 62 per cent were found to have a history of previous pulmonary disease and 84 per cent had gross and microscopic evidence of such disease. Moreover, it has been suggested, in part on the basis of analyses of necropsy data, that interstitial pneumonitis has been increasing within recent years (5, 12, 21), with the implication that this might serve as the background for an increase in bronchiolo-alveolar tumors.

Turning again to the acinar atypical proliferation associated with scleroderma and "diffuse sclerosis," it is remarkable that in so rare a condition at least 6 instances of pulmonary carcinoma have been reported (68, 108, 139). Of the total, 1 was an "oat-cell carcinoma," 1 an adenocarcinoma, and no less than 3 were reported as bronchiolo-alveolar tumors by Zatuchni *et al.* (139), although the illustrations reveal these to be relatively undifferentiated. In all of these patients there was a striking degree of acinar atypical proliferation associated with the clearly neoplastic process.

Considering a wider sphere, honeycombing not associated with obstruction of bronchi and which involves superior and posterior portions of both the upper and lower lobes occurs in approximately 20 per cent of patients with malignant pulmonary neoplasms, and in less than 3 per cent of persons of comparable age and sex without tumors (93). When there was honeycombing, bronchiolar carcinoma and adenocarcinoma occurred in approximately 25 per cent, or about twice as frequently as when honeycombing was not present. In view of the capacity of the epithelium in these acini to undergo squamous metaplasia, it is not surprising that many of these tumors were epidermoid. The occurrence of tumors in familial "cystic disease" of the lung has been reported by McKusick and Fisher (88). The proliferations reported by Gray and Cordonnier (52) and by Womack and Graham (134) in "cystic disease" would now probably be considered benign, contrary to their interpretation.

These observations suggest that pulmonary tumors, and more particularly bronchiolo-alveolar carcinoma, can arise in association with more or less widespread *acinar atypical proliferation*, which in itself

is to be regarded most reasonably as a regenerative process that occurs in response to a wide variety of agents.

It has already been remarked that bronchiolo-alveolar carcinoma, as well as other primary pulmonary neoplasms (38, 41, 47, 86), appears also to occur more or less marginally in relation to large scars in the lung (Plate 8, *B*), but that the presence of vessels obstructed by tumor makes it difficult sometimes to be certain that the scarring did not in fact result from infarction of the tumor (9, 59). Raeburn and Spencer (105, 106, 121), in particular, have been interested in the relation between pulmonary scarring and tumors and have reviewed previous observations; tumors in their earlier reports (105, 106) were not of bronchiolo-alveolar type.

Further studies are necessary to establish the relation of organizing pneumonitis, atypical proliferation, and scarring of various pathogeneses to the appearance of lung tumors in general and of bronchiolo-alveolar carcinoma in particular.

Histogenesis

The observations cited in an earlier section indicate that bronchiolo-alveolar carcinoma is commonly associated with scarring and atypical proliferation in the lung, but the question whether the cell of origin is in the lining of bronchioles, of alveoli, or of both still remains. Most of the available evidence favors the first (61, 62, 77, 79, 82, 83, 102):

(1) The cells of the tumor are certainly more like those of bronchioles than those of alveoli in the normal state, particularly in the frequent presence of mucus, and in the occasional presence of cilia.

(2) When alveoli acquire an investment of tall lining cells, even in nonneoplastic disease this can often be demonstrated unequivocally to have grown in from more proximal air spaces by any of several routes (15, 61, 80).

(3) In the search for histogenetic clues, it is more relevant to examine the isolated form than the multinodular, in which replacement of epithelium of bronchioles and the investment of a mass of surrounding alveoli can be interpreted simply as evidence of aerogenous metastasis. In the former, the lesion is usually symmetrically arranged about a particular bronchiole as a center in such a way as to make implausible any suggestion that "alveolar epithelium" could have extended proximally from a focus in the periphery (Plate 6, *B*). It is in the wall of such a bronchiole that considerable desmoplastic reaction may occur, while there is less fibrosis in the distal air spaces, including alveoli, where implantation of epithelium has occurred more recently. This

greater scarring in what has been soundly established as the primary nodule on radiographic evidence has been mentioned as a differentiating feature from the disseminated lesions. However, scarring may *sometimes be observed even in the latter.*

(4) In certain tumors, the cells lining the bronchiole of origin are piled up or thrown into papillary masses not seen elsewhere (Plate 7, *A*).

(5) Hutchison (64) has also cited the gradual transition of the lining epithelium of some bronchioles into what is clearly tumor as evidence of an origin there. Similar forms, apparently "transitional" to flattened cells lining distal air spaces, can commonly be identified, however, at the margins of the lesions where true alveoli form the stromal support. The interpretation of "transitional" forms is subjective, and any conclusions which may be drawn in regard to the origins of cells are notoriously tenuous. Such conclusions are best viewed under the legal principle: *pater semper incertus est.*

An argument in support of an origin from alveolar lining cells, while more tenuous, cannot be entirely discarded (2, 69, 126). Although the presence of a lining of columnar cells in the alveoli does not necessarily indicate an origin *in situ* (132), some observations do suggest this possibility. Where alveoli abut upon relatively rigid and immobile structures, a palisade of tall lining cells appears. This occurs sharply along the line of contact in alveolus after alveolus and there is no continuity with the epithelium of bronchioles, a fact that must always be established on the evidence of serial sections correctly interpreted. This is not always an easy task when the observer is dealing with such small structures.

It may be somewhat futile to argue the point of bronchiolar versus alveolar origin of these tumors, since it appears from the studies of Waddell (129) that both the distal branches of the bronchial tree and the alveoli are derived embryonically from mesoderm, much like the proximal segments of the nephrons. Although certain of the ultimate lining cells seem to respond differently to various stimuli than others, all can be altered in disease.

It may be concluded tentatively that while the bulk of evidence suggests an origin of these tumors in epithelium of the bronchioles it is impossible to deny alveolar lining cells as a possible source.

Unicentric or Multicentric Origin?

The early tendency to consider these tumors as originating in many foci (27, 115) has come to be questioned more and more. It is now

well established that at least some tumors with histologic features typical of the lesions when widely disseminated in the lung can occur also in a single focus. Such a focus can be detected in survey films of the chest even in patients who are entirely unaware of their existence (3, 12, 32, 101, 109, 110, 123, 125, 130). When removed at this stage, there has been no recurrence in a considerable number. In others, the tumor has ultimately become disseminated, apparently from a solitary lesion, while under radiographic observation during a period of many years (12, 67, 101, 112). Sometimes, the spread is local at first, and then involves the opposite lung. The lesion considered primary on this radiographic evidence may possess gross and microscopic characteristics different from the other lesions, as listed earlier. These characteristics will be missed in inverse relation to the observer's competence and experience in pathologic anatomy. A deep puckering of the pleura is often a useful clue to the position of the primary lesion. Furthermore, tumors metastatic from other organs can spread in a manner very similar to the primary bronchiolo-alveolar tumor, as emphasized by Herbut (61) and by Eck (32).

The possibility remains, however, that some of these tumors can arise in more than one center. Certainly, the atypical proliferation which may precede the appearance of these tumors can involve simultaneously many foci in both lungs. Several studies, moreover, have indicated that the lung can give rise to multiple carcinomas, of diverse histologic structure and separate geographic origin (42, 43, 71, 87).

The tentative conclusion can therefore be drawn that the diffuse or multinodular form of bronchiolo-alveolar carcinoma can merely represent a mode of extension within the lung of a tumor arising in a small, usually well-differentiated peripheral primary adenocarcinoma (32, 127).

Conditions in Animals Resembling Bronchiolo-Alveolar Tumor

Epithelial hyperplasia or neoplasia (it is often difficult to decide which) in the distal air spaces is well known to be common in many species of animals. The similarity of this process to bronchiolar tumors in man has attracted attention, especially since Bonné's report in 1939 (14). In particular, clues have been sought in observations on animals to the disease in man.

Multiple peripheral pulmonary tumors of acinar structure have been induced by the subcutaneous injection of carcinogenic agents, e.g., methylcholanthrene, in mice, a species in which such tumors

occur spontaneously. These tumors can metastasize. Grady and Stewart (51) concluded that they were of "alveolar epithelial" origin. Remarkably similar, but nonmetastasizing, are acinar proliferations which have been found in mice surviving injection with human influenza virus (124), in cattle by exposure to oxides of nitrogen (113, 114), and in guinea pigs infected with BCG (40). Their spontaneous occurrence has been observed in rats (121), horses (26), chinchillas (59), hamsters, and dogs (Plate 9, *A*), among other species (31). Apparently, the lungs of many species of animals react by marked atypical proliferation in response to diverse stimuli.

The greatest interest has been attracted by an apparently infectious disease of sheep in Africa named jagsiekte, and by a similar condition in this species that occurs in Iceland, Montana, and parts of South America. The descriptive term "adenomatosis" has been used for the lesions in the lung. An excellent review of this subject is that of Duran-Reynals and associates (31).

According to Cowdry (20), who early made careful histologic studies of this disease in Africa, the earliest lesion is usually interstitial thickening of alveoli. Parenthetically, a similar interstitial pneumonitis has been described in the chinchilla as a prelude to the development of "adenomatosis" (59). These observations recall the possible relation of interstitial pneumonitis and atypical proliferation to bronchiolo-alveolar carcinoma in man already discussed. Cuba-Caparó and co-workers (22) in studies of the lungs of sheep slaughtered for meat in Peru, found lesions limited to a lobe and 2 cm. or less in diameter. This, too, suggests origin in a single focus, and that the widely disseminated form of the disease usually described is, in fact, a late stage.

In fully developed lesions, the epithelium is usually of regular, tall, columnar type, mucus producing, with rare or no mitoses. The similarity to the better differentiated forms of bronchiolo-alveolar tumor is indeed striking. The cells are supported in part by a stroma of alveoli (Plate 9, *B*). Desmoplastic reaction, however, is also present in some foci. Although Cowdry (20) considered the alveolar epithelium to be the source of the neoplasm, he admitted that the lining cells of bronchioles also participate in the proliferative process, with the formation of papillary growths (Plate 10, *A*), and this has been confirmed in Icelandic sheep by Dungal (29), and in the Peruvian disease by Cuba-Caparó *et al.* (22).

The form of the disease that occurs in Peru at altitudes above 10,000 feet appears to be truly neoplastic and is known to metastasize (Plate 10, *B*). Only Aynaud (6) had previously reported metastases in "adenomatosis" of sheep. Cuba-Caparó *et al.* (22), who have extensively

studied the Peruvian form, observed metastases in 3 of 38 sheep with advanced disease. In another group of 20 animals with advanced clinical symptoms, Paredes (101a) in the same laboratory had found 4 with metastases. No instance of spread beyond the mediastinal nodes is on record.

Although there is abundant evidence that the ovine disease is infectious, no specific agent has as yet been identified, nor has it been possible to transfer the disease to other animals, such as mice, rabbits, or guinea pigs (29). de Kock's (26) attempts to produce the disease in this species with carcinogenic agents also were not successful. The observations upon these animals are of intrinsic interest, and may provide a fertile field for further study.

Etiologic Factors in Man

The search for an etiologic agent in bronchiolo-alveolar carcinoma in man has been pressed, although nothing has been noted to suggest its contagious nature except the morphologic similarity in some instances to ovine adenomatosis. Bronchiolo-alveolar tumors have been reported among those in close contact with sick sheep, for example by Heimann and Samuel (57), but these are certainly uncommon. Search for viruses has invariably been fruitless (25, 50, 81, 116, 135).

Bronchiolo-alveolar tumors have been reported in persons who had been exposed to beryllium (120), or who had received thorium dioxide (1), or in whom a lipoid pneumonia had been caused by nose drops (136), but no common factor has emerged. Several patients have had more than one carcinoma (39, 135), but again this is an infrequent coincidence. The only contributing factor appears to be the nonspecific one of chronic pneumonitis, and the associated atypical proliferation which has been discussed, and which can be the result of innumerable noxious agents.

The one common feature in all of the discussion just cited appears to be the proliferation of epithelium in the distal air passages. It is possible, however, that this is only one necessary factor in the genesis of neoplasia.

Extension within Lung

Hematogenous.—Compression (Plate 11, *B*) and invasion of pulmonary arteries are frequently observed, even in well-differentiated bronchiolo-alveolar tumors (8, 82). This cannot account for more than a small part of the observed multinodular or pneumonic spread, since the pulmonary arteries are more or less "end-vessels," supplying a par-

ticular section of the periphery, while the veins represent a path of dissemination *from* the lung.

The compression, often to a state of occlusion, or the invasion of vessels may account for the necrosis and late fibrosis observed in some of the isolated nodules.

Lymphogenous.—Invasion of lymphatics about the broncho-arterial rays, veins, septa, and pleura of the lung occurs in at least 50 per cent (123), and has been reported to be as high as 75 per cent (119) in some series. Eck (32) and Tauchi (127), especially, have stressed the importance of the lymphatic pathways in the dissemination of these tumors within the lung. It is difficult to understand why the regional lymph nodes are not invariably involved in the presence of the often extensively invaded intrapulmonary lymphatic channels.

Penetration to larger bronchi can occur by means of lymphatic pathways; a bronchoscopic biopsy may then reveal the tumor (123).

Aerogenous or surface spread.—To many who have considered this problem, the evidence of aspirative spread has appeared compelling (7, 61, 64, 65, 77, 79, 83, 112). Furth (44) has shown that tumors in animals can be transplanted by intratracheal insufflation. In man, aspirative spread of papillomas of the larynx to the lower respiratory tract seems well established (63, 82). Cain (16) has cited an instance of apparent penetration of a metastasis from a bronchial lymph node into a bronchus with a pneumonic form of propagation within the lung of that side. The occurrence of "carcinomatous pneumonia" has been reviewed by Rössle (111) for both primary and metastatic tumors within the lung, and he has considered in more general terms the spread of malignant neoplasm along surfaces. Others (11, 104) have reported primary lung carcinomas to "masquerade" as bronchiolo-alveolar tumors. Herbut (61) in a systematic review, reported that 6 of 125 cancers metastatic to the lung had an "alveolar" distribution; 4 were from the large intestine, and 1 each from the pancreas and gallbladder (Plate 11, *A*). Ovarian tumors (16) and breast tumors (6), and even hypernephroid carcinomas (74) have been found to behave similarly.

Pleural involvement.—The pleura is commonly closely approached by tumor, but actual invasion with seeding as seen in other malignant pulmonary tumors and with metastases is uncommon. During the course of the disease, serous or serosanguineous pleural effusion was reported in 10 per cent of patients by Decker (25), in 17 per cent by Storey (123), and in 9 of 33 patients by Watson and Smith (130). By the time of death from the disease, effusions, adhesions, and other changes are encountered more commonly than is suggested by these

figures. Extension to pleura can occur locally with the formation of a thick-walled pocket outlined by invaded visceral and parietal pleura and filled with cloudy mucoid material. In the multinodular forms, the lesions are usually evident by palpation of the pleura, and may actually be visible. The more superficial of the larger nodules may be umbilicated and attached to the visceral pleura. Lymphatics filled with tumor tissue can sometimes be seen as a beaded tracery of pearly cords within the thin and shining serous membrane covering the lung.

Extrapulmonary Metastases

Incidence data regarding metastases vary somewhat depending on the criteria used in defining bronchiolo-alveolar tumors and on the size of the series, but most observers are in agreement that at the time of death metastases will be found in 50 to 66 per cent (32, 53, 98, 123, 125).

In the largest collected group the incidence was 54 per cent (123); of these, slightly more than a third spread within the thorax, predominantly to mediastinal nodes, another third had both local and distant metastases, and in the remainder there was distant spread only. Actual invasion of the pleura was found in 17 per cent of the patients, and of the pericardium in 12 per cent. Among distant metastases, extension to the liver was most common (37 per cent), with involvement of the bones, adrenals, and brain each in approximately one-quarter of the cases and of the kidneys in just under a fifth.

In some series, in which the patients were largely those selected for operation, the incidence of metastases was not as high, for example 2 of 12 patients in the group reported by Good *et al.* (50). Although 25 of the 33 patients in Watson and Smith's series (130) had metastases, only 4 of 10 of the solitary type were found to have metastasized to regional lymph nodes.

Natural History

Course of lesions apparently localized when first seen.—Among the most interesting features of the variable natural history of these tumors is the long dormancy, or very slow growth of some of them, particularly those presenting as isolated nodules in the roentgenogram. A considerable number of patients with such lesions have then survived for long intervals after surgery. In the cases reported by Farber *et al.* (36), Arany (3), Upensky (128), and Rigler (109), the known duration before surgery was from 6 to as long as 14 years.

In others, in whom the lesions were known to have begun as isolated ones, generalization ultimately occurred. Schuster's (112) patient had an initial small lesion, which over a 4 year period spread in the "pneumonic form" bilaterally. In 1 patient with an 8 year history, the lesion recurred on the side of the first lobectomy; a pneumonectomy was performed but the patient died 2 years and 8 months later (case 8 of Overholt *et al.* (101)). Another patient was still asymptomatic 8 years after the lesion was first noted as a small infiltrate in the right upper lobe and 6 years after its removal, although bilateral small lesions were *in evidence (67). Delarue and Graham's (27) patient was asympto*matic for 4 years after a lobectomy, but then the lesion recurred in the remaining homolateral lobe; 2 years after a pneumonectomy on that side, there was no further sign of recurrence. Another lived 5 years after pneumonectomy for a lesion 8 cm. in diameter, but then succumbed to the spread of the disease (12).

Other tumors, apparently isolated when first detected, progress with greater rapidity, e.g., case 2 described by Storey (122) and the case illustrated in Plate 2.

Course of lesions already disseminated when first seen.—The presence of disseminated lesions of bronchiolo-alveolar carcinoma usually means an inexorable progress of the disease to death within 2 years. The most notable exception is the case reported by Ziegler (141); the patient was known to have bilateral scattered lesions for 14 years, and these were all the more remarkable because calcification was easily visible on the roentgenograms. At death, there were metastases in the hilar lymph nodes and diaphragm. Other examples of survival for more than 3 years with the generalized disease have been reported (35, 67).

A strikingly rapid course has been demonstrated in some patients. In 1, bilateral disease was discovered 6 weeks after a chest film had been interpreted as normal (37). Although progress in others has appeared almost as explosive (1, 64, 65, 97), this does not rule out a long latency, perhaps in a single focus, before the bilateral process became evident.

Correlation of course with tumor's histologic nature.—It is clear that much has still to be learned regarding the vagaries of the course of these tumors. Many of the best differentiated have been bilateral and extensive when first discovered, with a short course, as exemplified in the first reported case of the "pneumonic" type (97). The well-differentiated nature of the tumors in at least some of the patients who have survived 5 years after resection has drawn comment (119). However, it is still uncertain whether it is the localized state of the lesion or its histologic structure which is the more significant element in prognosis.

CLINICAL FEATURES

Age and Sex Incidence

Although the average age of 54 years quoted in one survey (122, 123) of over 200 patients is not too far from that of bronchiogenic carcinoma, the distribution is wider. According to Griffith and associates (53), 11 per cent of cases occur in the third and sixth decades, and 5 per cent in the second and seventh decades. The disease occurs at a relatively early age, and the extremes reported have been 16 and 89 years.

The sex ratio, in contrast to that of patients with the predominant epidermoid and undifferentiated lung tumors, is only slightly in favor of the male (53, 123).

Symptomatology

Localized form.—In general, 7 per cent of all patients with bronchiolo-alveolar tumors have no complaints (123), but the localized form specifically is commonly asymptomatic, or the symptoms are minimal and vague (3, 12, 32, 109, 110, 123, 125). The usual absence of significant atelectasis, infection, and invasion of the pleura accounts for this insidious early course. Of the 15 patients reported by Overholt and co-workers (101), 9 were asymptomatic, and the diagnosis in 13 was made on the basis of survey films; this represents an especially favorable clinical group, in which 8 were classified as "coin lesion," and who did well after surgery. In another group of 13 patients, 3 had no symptoms, but this group included some patients with advanced disease (92). When it is recalled that most cases are not recognized until they have become bilateral, and that it is likely that many, if not all, must have begun in a single focus which can persist as such for long periods, the ominous silence of this disease in its early phases will be appreciated.

Signs and symptoms in general.—The trend suggested by the extensive analysis of Storey *et al.* (123) was confirmed by their observations on their own patients, and is further substantiated by several other large groups in other reports (53, 130). Only 30 per cent have symptoms for less than 6 months, while almost 1 in 4 have some complaint referable to the chest for 2 years or more.

Cough, somewhat more often productive than not (53), is the most common first sign, and ultimately occurs in at least 70 per cent of patients known to have the disease. The sputum is usually described as white and frothy, but hemoptysis appears in approximately 1 of every

4 patients. Really large amounts of sputum, more than 100 cc. daily, are produced in a similar proportion, and, rarely, the volume can approach 4 liters daily. The sputum may be remarkably thin and watery when produced in such large amounts. In 1 patient whose daily sputum production was as much as 2,000 cc., even exceeding the urinary volume, Levinsky and Kern (81) found actual evidence of dehydration, with the hematocrit increased to 60 per cent and the total plasma and blood volumes diminished. The total plasma protein and chloride contents were strikingly reduced, but the potassium was elevated. The protein content of the expectorate varied from 0.26 to as much as 1.1 Gm. per 100 cc. The blood protein concentration was normal at first, but later fell to 5.8 Gm. per 100 cc.

In the review of Storey *et al.*, dyspnea is recorded as an *ultimate* symptom in 48 per cent of patients, but this is a minimal figure, since some of the patients had relatively little involvement of the lung when the history was recorded. Distant metastases, especially to the brain, however, can occur before dyspnea becomes evident.

Thoracic pain is a complaint in 1 of every 3 patients as the disease advances. This symptom can occur in the absence of metastases to the bones, or of pleural involvement.

Fever is mentioned as a prominent finding at some time during the course in 9 per cent of the patients, but in minor degree it is certainly more frequent.

Diagnosis and Differential Diagnosis

Since in some 50 per cent of patients the lesions are bilateral when first seen, it is not surprising that in a large proportion the initial diagnosis is tuberculosis, sarcoidosis, silicosis, bronchopneumonia, metastatic carcinoma, disseminated mycosis, or bronchiectasis, in more or less that order of frequency (8, 122, 125). Many patients are hospitalized and studied for the first time in tuberculosis sanatoriums (103) (*see also* Plate 2, *A*).

Physical signs are even less specific than the clinical symptoms. In fact, in more than a third of the cases in the series of Watson and Smith (130) objective signs were not detected. The high proportion of solitary nodules in their group accounts for this finding. When present, the signs may be those of pulmonary consolidation, with or without rales. Signs of pleural effusion or pleural thickening exist late in the disease in roughly 20 per cent of the patients.

Radiographic features.—In the experience of Smith *et al.* (119), the bronchiolo-alveolar tumors first present on the roentgenogram

most commonly as a zone of increased density of circular outline; this is confirmed by Storey (122). Watson and Smith (130) described these shadows as tending to be less dense, less homogeneous, and less sharply outlined than those of metastases, which they otherwise resemble.

In approximately 50 per cent, the disease is bilateral when first seen, and in 20 per cent the lesions have the appearance of multiple, rather sharply outlined nodules within both lung fields. Only in 3 per cent does the lesion appear to be parahilar on the roentgenograms (123). Again, none of these features is diagnostic of bronchiolo-alveolar tumor. Visible calcification in the lung fields is against this diagnosis. Calcified psammoma bodies, so often seen under the microscope, do not provide sufficient radiographic contrast to be distinguished as such. Ziegler (141), however, has reported an exceptional instance of striking calcifications within multiple nodules of a long-persistent, well-differentiated bronchiolo-alveolar tumor.

Zheutlin, Lasser, and Rigler (140) have described a characteristic, but probably not pathognomonic, sign in the bronchograms of patients with the disseminated form. This consists of a uniform, strikingly threadlike narrowing and elongation and apparent rigidity of smaller bronchi in the involved pulmonary areas (Plate 12, *A*). These tubes seem filled rather than coated with the opaque medium, while their distal ramifications remain empty, giving a "leafless tree" appearance. These changes were observed in 6 of the 7 patients in the original report. The explanation of this change is seen in the desmoplastic reaction in the walls of the bronchi, the neoplastic epithelium of which may or may not narrow the lumen (Plate 12, *B*).

Microscopic diagnosis.—It is evident that a specific diagnosis can only be made with the aid of the microscope. Up to the time of the review by Storey *et al.* (123) this was accomplished only at the postmortem examination in almost half of the cases, and after resection of tissue in 23 per cent.

The least traumatic method for the patient is that of cytologic examination of the sputum or bronchial secretions. When sputum is present, and especially in the disseminated form of the disease, the exfoliation is likely to be abundant (36, 119). In a series from the Mayo Clinic (92), diagnostic cells were found in 7 of 11 patients (63.6 per cent). Overholt *et al.* (101), reported this procedure to be of no particular value; their series, however, comprised predominantly isolated lesions.

As seen in smears, the appearance of the cells often deviates only slightly from that of normal columnar epithelium (Plate 13, *A*). The nuclei are smaller than those of less well-differentiated adenocarci-

4 patients. Really large amounts of sputum, more than 100 cc. daily, are produced in a similar proportion, and, rarely, the volume can approach 4 liters daily. The sputum may be remarkably thin and watery when produced in such large amounts. In 1 patient whose daily sputum production was as much as 2,000 cc., even exceeding the urinary volume, Levinsky and Kern (81) found actual evidence of dehydration, with the hematocrit increased to 60 per cent and the total plasma and blood volumes diminished. The total plasma protein and chloride contents were strikingly reduced, but the potassium was elevated. The protein content of the expectorate varied from 0.26 to as much as 1.1 Gm. per 100 cc. The blood protein concentration was normal at first, but later fell to 5.8 Gm. per 100 cc.

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Radiographic features.—In the experience of Smith *et al.* (119), the bronchiolo-alveolar tumors first present on the roentgenogram

good a result as total pneumonectomy. Some patients have even survived 5 years after simple excision (119). If the tumor recurs after lobectomy, it may still be desirable, in hope of cure, to complete the pneumonectomy (27). Rather extensive disease involving most of a lobe is not necessarily fatal, if treated by pneumonectomy (50), but if more than one lobe is involved, even on the same side, the chances of later finding contralateral disease are great.

PROGNOSIS

The vagaries in course of the untreated case have already been described. It remains urgent to establish the diagnosis of any lesion within the lung, whether or not it is causing symptoms; when other means fail to provide a reasonably conclusive diagnosis, thoracotomy is necessary. A comparison with any previous films that may be available is desirable, but the apparent quiescence of some rounded lesions is not a guarantee of benignancy.

Results after surgical treatment have varied widely, and the explanation lies only partly in the apparent localization of the lesion after treatment. Overholt *et al.* (101) have called bronchiolo-alveolar tumors "favorable"; 7 of their 15 patients were alive and well without signs of recurrence 2 or more years after resection, and there were 3 others with a postoperative follow-up of 1 to 1½ years. Storey (122) is also optimistic regarding prognosis as contrasted with that in other carcinomas of the lung. He and his co-workers (123) state with some confidence that any patient who is alive and well without evidence of recurrence after careful study within 2 years, is unlikely to show progress of the disease later. Of a group of 33 patients reported from the Memorial Hospital, 16 received surgical treatment, 9 of them by total pneumonectomy; 10 were living and 2 had survived for more than 5 years after operation (130).

Much more disappointing were the results of Mears *et al.* (92): 15 operations were performed in their 13 patients; 10 had lobectomies and 3 had pneumonectomies; only 2 were alive without recurrence, 1 at 4 years, and 1 at 1 year after operation; 2, however, died soon after operation, and 2 others succumbed to unrelated causes.

Davis *et al.* (24) also have a poor impression of the prognosis in this disease. They encountered 9 bronchiolo-alveolar tumors among 215 patients with solitary pulmonary nodules. All but 3 of the former were dead or were reported in process of dying; only 1 of the 3 was a long-term survivor; resection in the other 2 had only recently been performed at the time of reporting.

nomas, but are somewhat more variable and contain more prominent nucleoli than those of normal cells. Multinucleated cells are present in small numbers in some cases (119). Hatfield and Hill (56) have mentioned as characteristic an arrangement of cells packed into elongated cylinders, but this appearance can occur in some adenocarcinomas (82) (Plate 13, *B*). Cell clusters do occur characteristically in the sputum of patients with bronchiolo-alveolar tumors, but these, too, can be seen even with well-differentiated metastatic adenocarcinomas (Plate 13, *C*).

Tissue has also occasionally been obtained by bronchial biopsy, as in 2 patients reported by Good *et al.* (50) and in another of Watson and Smith's (130) group. Extension to proximal bronchi by lymphatic routes has already been mentioned.

Aspiration biopsy through the chest wall is unjustified except possibly in the disseminated form of the disease, but can yield tissue diagnostic of bronchiolo-alveolar carcinoma (119). A thorough search of sputum for neoplastic cells should first be performed.

Lung biopsy through a small intercostal incision has also been employed successfully, but has its dangers, and, as Storey *et al.* (123) point out, is justified only because it may yield a clue to the existence of a remediable disorder, rather than bronchiolo-alveolar tumor.

TREATMENT

To date, surgical resection has proved to be the only successful method of treatment. Radiotherapy has not significantly interrupted the inexorable course of the disease once it has become disseminated. It was tentatively thought to be palliative by the group (119) at Memorial Hospital, New York, but later discarded (130). Levinsky and Kern (81) found some possible improvement as suggested by a decrease in the amount of sputum produced, but this proved to be temporary. "Cytotoxic agents," such as the nitrogen mustards, which have been used to date, also have not proved effective (50, 61, 73).

Skorpil, in 1936, was the first to treat a patient surgically, and he described this case in his report of 1941 (117). It is noteworthy that his patient was alive and apparently well 5 years after a lobectomy, although 2 hilar lymph nodes were found to be greatly enlarged as a result of metastases. The case surgically treated by Griffith *et al.* (53) in 1943 was the second.

Opinions have varied regarding the extent of the resection to be performed. Overholt *et al.* (101) are of the opinion that conservative resection, i.e., lobectomy, in the case of localized lesions will yield as

Much remains to be learned concerning tumors of the lung in general, and bronchiolo-alveolar carcinoma in particular. We may look forward to further contributions to classification on the basis of histochemistry, electron microscopy, and other methods now under development. Perhaps these may ultimately illuminate also the puzzling tendency of these tumors to spread widely within, but to remain confined to, the lung. Further study of the natural history of the disease even by existing methods, with attempts to investigate more fully the apparent relation to atypical proliferation, may be useful. Certain factors responsible for the latter can perhaps be identified. It is also of interest to establish firmly whether one or both are increasing in prevalence, as some aver.

The similarity to "adenomatosis" of sheep is intriguing, and further effort should be made to discover the etiology and pathogenesis of this disease or diseases, as a possible clue to bronchiolo-alveolar carcinoma in man.

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CONCLUSIONS

The following credo regarding bronchiolo-alveolar tumors seems best supported by observations available at present:

Bronchiolo-alveolar carcinoma can be tenably defined as a well-differentiated adenocarcinoma, originating in the periphery of the lung, and tending to grow predominantly within it, supported in part by the stroma of distal air spaces. Bronchiolo-alveolar carcinomas so defined form approximately 2 per cent of all malignant lung tumors. Forms not clearly differentiable from bronchiogenic adenocarcinoma exist. Dissemination within the lung is predominantly aerogenous, but often also occurs via lymphatics. When metastases occur, they are usually confined to the thorax, but in 25 per cent of patients they may be widespread.

It is probable that the great majority of bronchiolo-alveolar tumors begin in a single focus, and then become disseminated in the lung to give the appearance of a multinodular, or pneumonic tumor; the latter is simply a variety of the former, with closer spacing of smaller nodules. However, multicentric origin of some lesions is possible. Most bronchiolo-alveolar tumors appear to originate in the epithelium lining bronchioles, but in some instances the lining cells of the alveoli cannot be excluded with certainty as a source. Bronchiolo-alveolar carcinoma is frequently associated with interstitial pneumonitis, or focal scarring, and the regenerative atypical epithelial proliferation accompanying these processes.

In the isolated nodular form, the lesion may persist quiescently for many years, or may become rapidly disseminated. Even tumors widely disseminated when first seen may have a variable course; some may progress very slowly, others may overwhelm available respiratory surface within a few months.

The condition is most usefully diagnosed when it is found simply as an isolated asymptomatic shadow on the roentgenogram. To establish the diagnosis under these circumstances, resection, preferably lobectomy, is usually necessary when the results of extensive clinical and laboratory studies have proved negative. To withhold surgery under these conditions is to place the patient's life in unnecessary jeopardy. Cytologic studies will only occasionally be positive in the isolated form of the disease, but, in competent hands, will usually yield diagnostic cells in the disseminated form. In the latter, there are also characteristic bronchographic signs.

Only surgical treatment has proved effective, especially if the lesion is present in a single intraparenchymal focus, but not if the lesions are bilateral.

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